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Title: 2021 R&D 100 Entry - EpiCast: simulating Epidemics with Extreme Detail

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2021 R&D 100 ENTRY

EpiCast

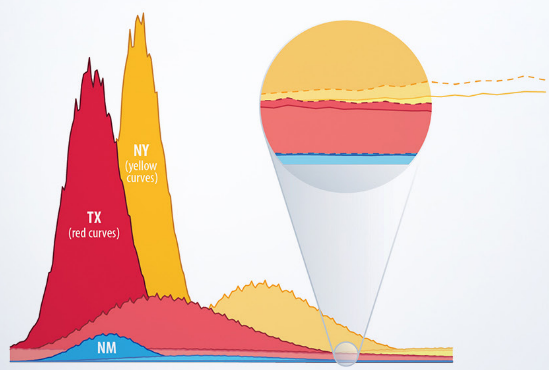
SIMULATING EPIDEMICS WITH EXTREME DETAIL

- Synthesizes entire populations to understand and **PREDICT** disease spread

- Models human behavior combined with **COMMUNITY** specifics

- Accounts for differences in infectivity resulting from viral **VARIANTS**

- Provides a fine-grained preview of potential **MITIGATION** strategies



Los Alamos
NATIONAL LABORATORY

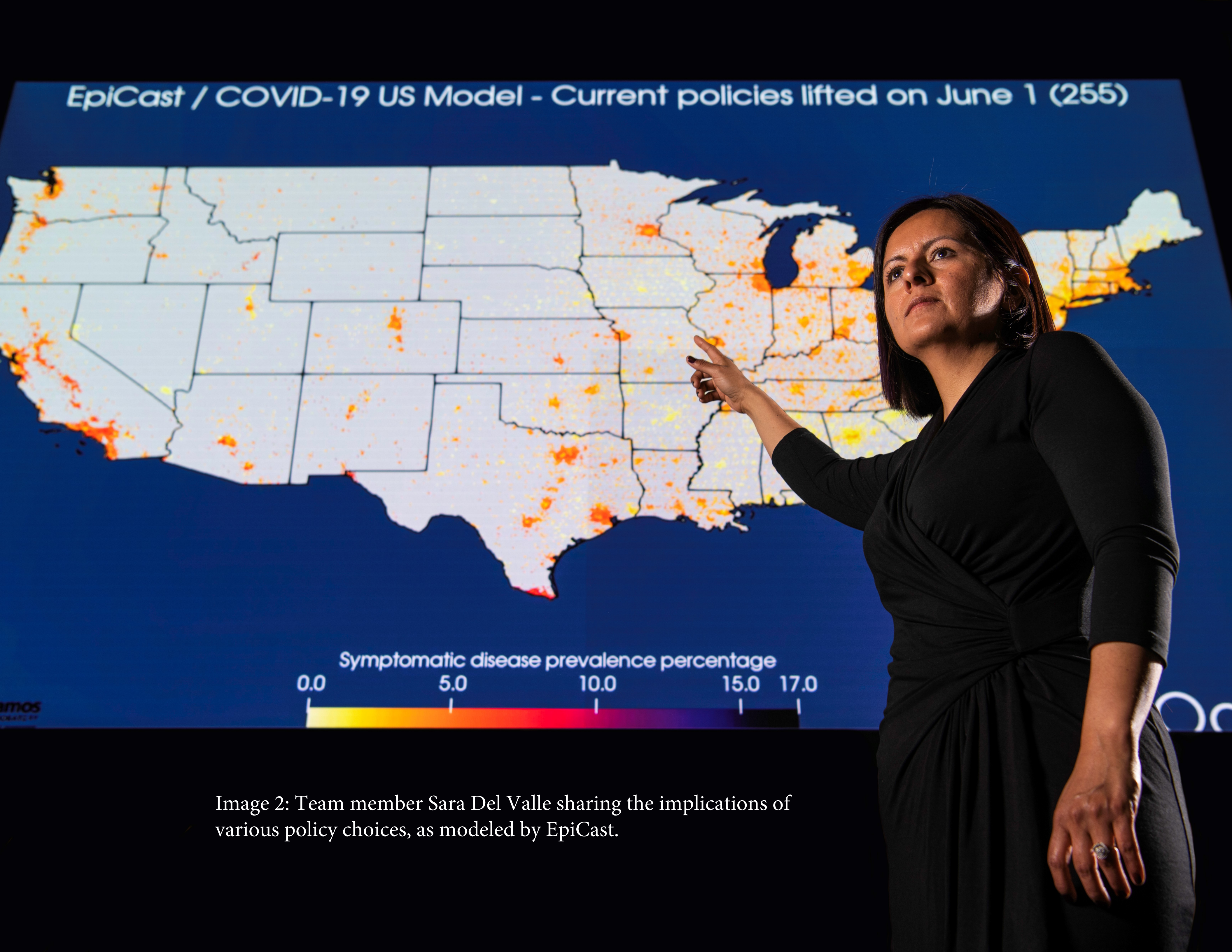


Image 2: Team member Sara Del Valle sharing the implications of various policy choices, as modeled by EpiCast.

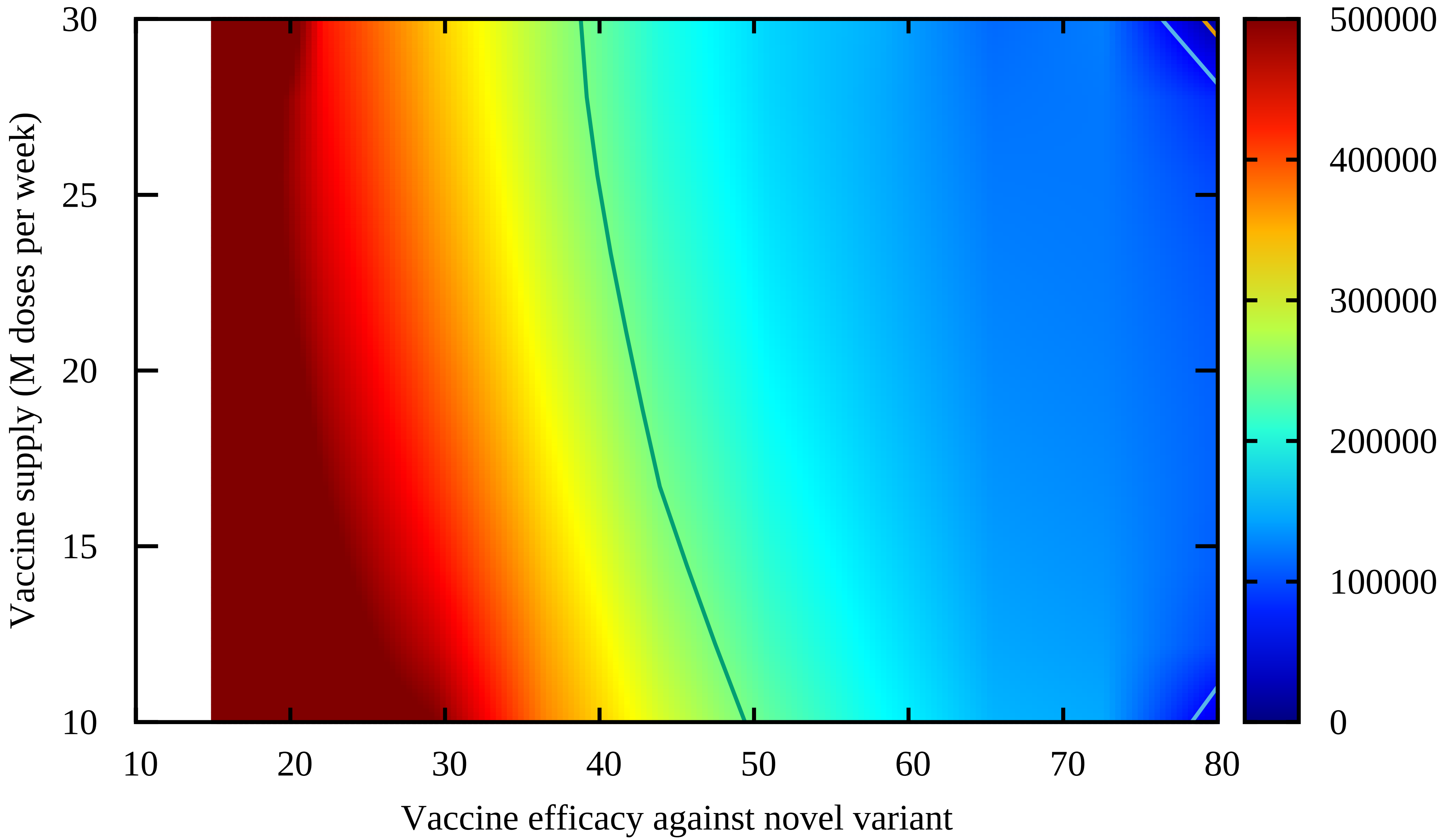


Image 3: EpiCast output plotting vaccine supply against vaccine efficacy. The figure shows how vaccine doses per week impact vaccine efficacy against a novel viral variant.

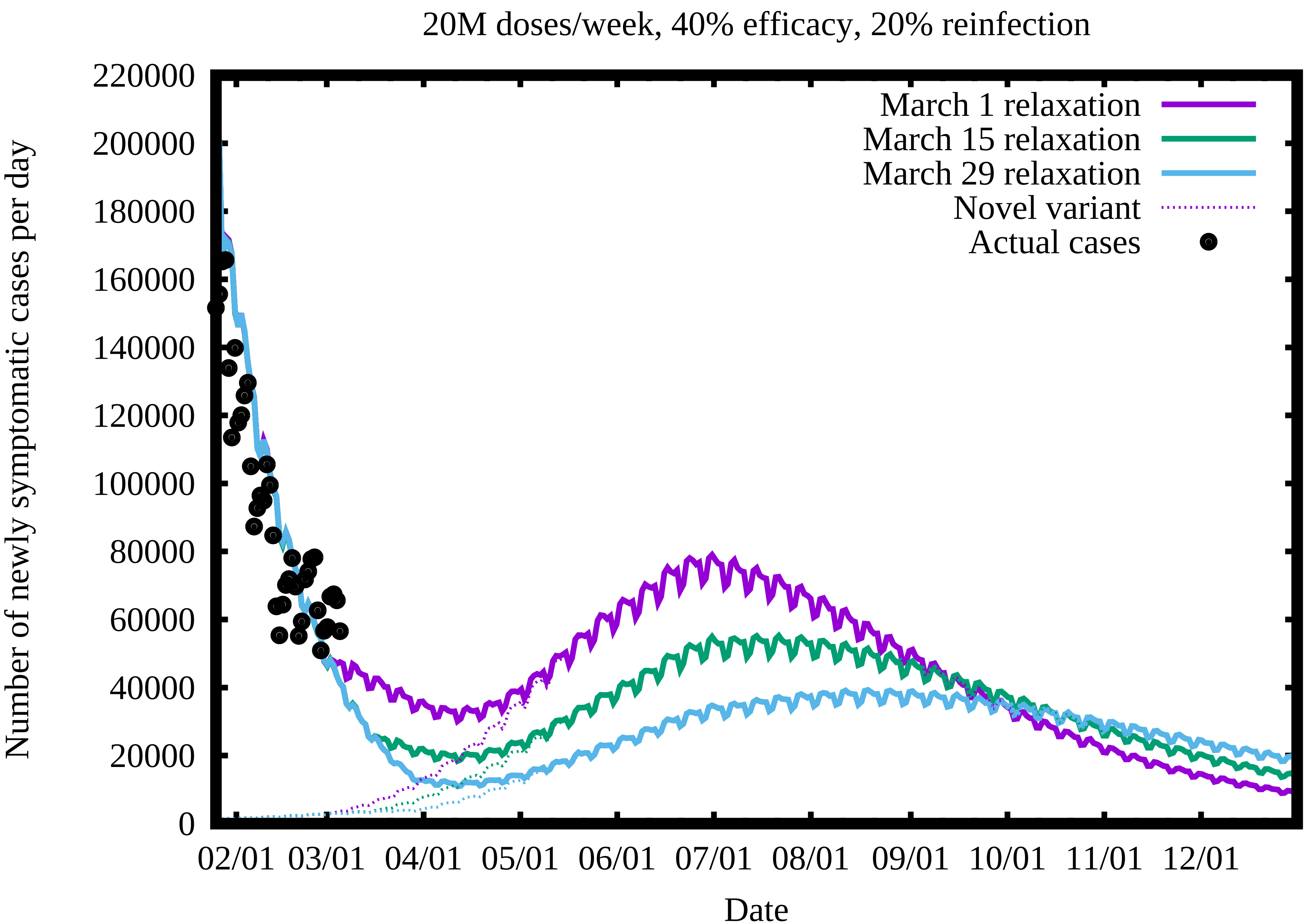


Image 4: EpiCast output projecting the number of new infections based on when mitigation measures are relaxed (March 1, 15, or 29).

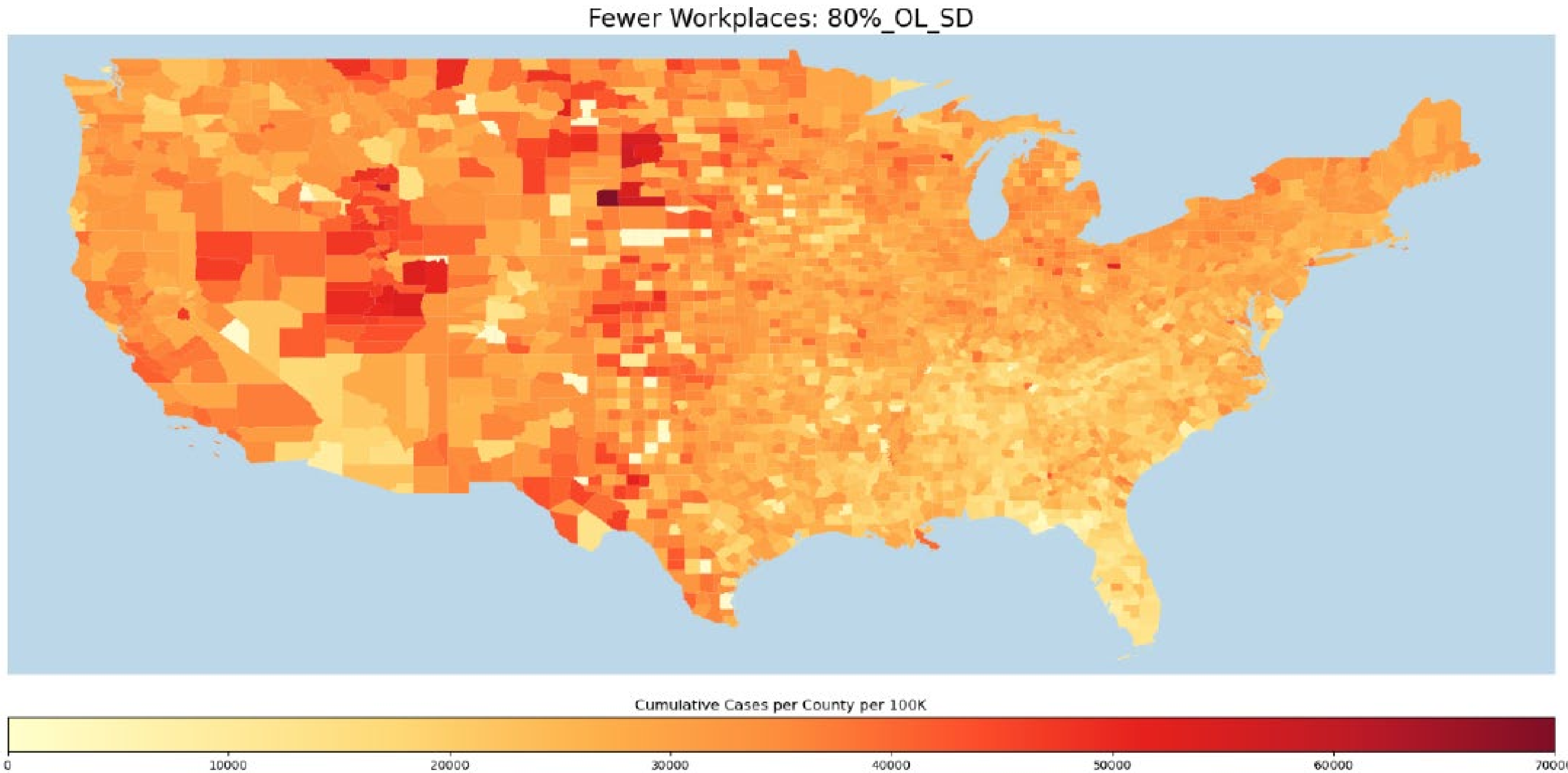


Image 5: EpiCast projections for cumulative cases per county per 100k. Simulation shows results if 80% of students attended school full time.

2021 R&D 100 Awards

Title of entry

EpiCast: Simulating Epidemics with Extreme Detail

LA-UR-21-

Category(ies)

- [x] Analytical/Test
- [ ] IT/Electrical
- [ ] Mechanical/ Materials
- [ ] Process/Prototyping
- [x] Software/Services
- [ ] Other
- [x] Special recognition: Corporate Social Responsibility
- [ ] Special recognition: Green Tech
- [ ] Special recognition: Market Disruptor - Products
- [ ] Special recognition: Market Disruptor - Services
- [x] Special recognition: Battling COVID

Name of primary submitting organization

Los Alamos National Laboratory

Name(s) of co-developing organization

None

Product/service brand name

EpiCast: Simulating Disease Epidemics with Extreme Detail

Was the product/service introduced to the market between January 1, 2020, and March 31, 2021?

☒ Yes

☐ No

If your submission is subject to regulatory approval, has the product been approved?

☐ Yes

☐ No

☒ Not applicable to this product

Price of product/service (U.S. dollars)

EpiCast is a custom service with personalized inputs and analyzed outputs, so pricing varies considerably depending on the tasking.

Product description

EpiCast is modeling software that generates a synthetic, representative population to simulate infectious disease transmission in the United States with extreme detail and granularity. The software models human behavior combined with community-specific information to provide a fine-grained preview of the effect of potential mitigation strategies for decision makers.

Indicate the type of institution you represent

Government Laboratory

Submitter's relation to entered product/service

Product Developer

Product Photos

Photo 1 - Cover

Photo 2 – Sara at the Powerwall

Photo 3 – USZ 1 figure

Photo 4 – Heatmap figure

Photo 5 – *medRxiv* figure

1. **What does your product or service do?**

You are walking through the grocery store when a stranger coughs. In late 2019, in a market on the other side of the world, someone may have heard a similar cough. Then, in an impossibly complex path, SARS-CoV-2 arrived in your canned goods aisle. Only one class of infectious disease models can begin to describe the winding chain of infections that led to this moment, and they typically run on high performance computers designed to model the billions of individual atoms in a nuclear explosion. EpiCast and models like it harness this computing power to represent millions of people and their unique behaviors to simulate the most likely course of a pandemic through a population. These realistic models of pandemic and human behavior are needed to inform decision makers as they plan mitigation scenarios.

Researchers have been deploying mathematical models to understand and predict disease spread for decades. In early February 2021, the Centers for Disease Control and Prevention (CDC) had received COVID-19 forecasts from 94 different models, and many were from SEIR-type models, which use differential equations and assumed transition rates to determine the relative number of people in general categories. These models get their name from how they categorize individuals: susceptible (S), exposed (E), infectious (I), and removed or recovered (R), but they have since evolved to include even finer categories, such as age, location, and vaccination status. These types of models assume that everyone in the model has an equal chance of getting infected, when in reality, demographics, behavior, and daily activities (among other factors) play an enormous role in this probability. As such, these SEIR methods are best suited for an epidemic that has already infected a large part of the population and is spreading, and they are less effective at describing the critical stages when only small numbers of people are affected, when an infectious disease first appears in a community, or when it is nearing extinction. In particular, SEIR models are less effective when additional variables dictate how a disease spreads in the population, for example if age or sexual orientation is a factor (e.g., HIV). For this purpose, researchers use the often far more sophisticated projection models, a

> Apart from SEIR and projection models, **statistical models** provide another means of understanding disease spread. Statistical models can provide quick, often less-detailed forecasts that rely on learning trends from high quality initial data about disease spread within a population.

technology that has its roots as early as the 1940s but only recently reached its apogee – with EpiCast.

EpiCast's earliest predecessors modeled disease spread within small-scale, structured communities in order to evaluate influenza vaccination strategies. The idea was to simulate a synthetic population of individuals, or "agents." Instead of relying on average behaviors, researchers could better capture heterogeneity within a given population. Limited computing power meant that early models could simulate communities of only 1000 to 2000 people within a reasonable time frame. Nevertheless, these models saw widespread use over the years, complementing traditional SEIR-type models, particularly when assessing the probability of outbreak of an emerging disease or its successful quenching. However, since they could only simulate a single community, questions about spatial spread or containment, for instance by limiting travel, remained unanswered.

Researchers understood the potential of this agent-based approach and continued developing this type of model, taking full advantage of advances in computing power. By the mid-2000s, agent-based simulations could apply enough computing power to connect geographically-distant communities based on tract-to-tract worker flow data, most notably in individuals' daily commute from home to work. Census data enabled the model to accurately represent these regular short-range mobility patterns, while Department of Transportation data on business and personal travel measured irregular longer-range mobility, even accounting for people on vacation. The model could now drop vacationers into different, specified communities for varying trip durations, simulating the contact patterns of a tourist. By the late 2000s, the model could accurately synthesize the day-to-day interactive patterns of ~300 million individual persons in the United States.

At this point in history, the world had not suffered a pandemic of catastrophic proportions in almost exactly a century, when the 1918 influenza pandemic caused tens of millions of deaths worldwide. (HIV/AIDS, which is termed a "global epidemic" rather than a pandemic by the World Health Organization (WHO), has caused a similar number of deaths since its arrival in

1981.) Many governments were concerned about the potential spread of avian influenza, but a worldwide pandemic seemed a remote possibility to most.

In early 2020, COVID-19 swept the globe. Governments attempted to “flatten the curve” through business shutdowns and stay-at-home orders, but the United States was hit hard. By the end of March, mere months after the virus first emerged in humans 7,000 miles away, the U.S. had recorded 192,300 cases and 5,300 deaths. While this unprecedented disaster sent shockwaves through every level of society and clouded an uncertain future, state and local governments turned to computational and mathematical epidemiology researchers to help formulate intervention strategies to limit the spread of the disease. Traditional forecasting models provided a reasonable understanding of how the near future was likely to look, but local policy makers and public health communities still struggled to understand how potential mitigations ought to be implemented. Decision makers needed a way to measure the impact of their policy choices—they needed better technology. EpiCast answered the call, bringing urgently needed answers to policymakers grappling with how to adjust school and business schedules.

EpiCast is fundamentally different from forecasting models because of its unprecedented depth of detail and the ease with which it incorporates new information and variables. Unlike traditional forecasting models that typically require statistics on disease spread within a region, EpiCast does not require prior data on transmission within a population to model an outbreak. This means that EpiCast can powerfully address “what-if” questions about hypothetical future pandemics, or inform mitigation strategies such as how to best deploy vaccines or antiviral drugs, implement social distancing measures, etc., during a current pandemic. Researchers need only input key variables about the disease itself, such as its infectivity, mortality, and how it spreads (airborne or otherwise). These data points are easily acquired once a disease has been identified clinically, but before widespread transmission, a crucial window of time for implementing mitigation policies. Of course, as more information becomes available, it can often be used to improve the model’s fidelity and accuracy.

EpiCast's key innovation is its ability to answer specific intervention-related questions whose answers guide policy. Forecasting models can tell you what will happen if you maintain the status quo, while EpiCast tells you what could happen if you implement any number of a wide range of mitigation strategies. A policymaker can ask "What would happen if we reopened schools at reduced capacity?" or "How might different vaccine allocation strategies (i.e., different prioritization approaches) impact the spread of the disease?" EpiCast allows incredible detail in adjusting these variables; policymakers can even explore the implications of opening specific buildings or industries: "What would happen if no restaurant servers wore masks?" or "How is the virus more likely to enter a school setting: from a teacher or from a student?" Questions like these and their detailed answers are vital for scientifically guided mitigation strategies, and traditional forecasting models do not provide the answers.

Example Questions EpiCast can Answer

- How is social distancing affecting transmission?
- What would happen if K-8 schools reopened?
- What is the impact of different mask compliances (0-100) across different counties and states?
- What if a new variant is 3x more infectious?
- How will local and long-distance travel restrictions affect spread?
- How will reducing restaurants to 25 percent capacity affect spread?
- What if we vaccinate school teachers after healthcare workers?

In August 2020, EpiCast projected daily case counts in three states (TX, NY, and NM) under four potential school reopening scenarios: (1) Business as usual (tall peaks), (2) 80 percent onsite learning (smaller peaks), (3) 40 percent onsite learning (nearly flat), and (4) Schools closed (flat lines). These projections highlight the impact of even slightly reduced onsite learning, and provide a scientific basis for the policy that would go on to impact the education and safety of millions of students. Currently, the EpiCast team is working with the New Mexico Department of Health (NMDOH) and the U.S. Centers for Disease Control and Prevention (CDC) on school reopening scenarios, relaxation of public health orders, vaccine distribution scenarios, and evaluating the impact of non-pharmaceutical interventions.

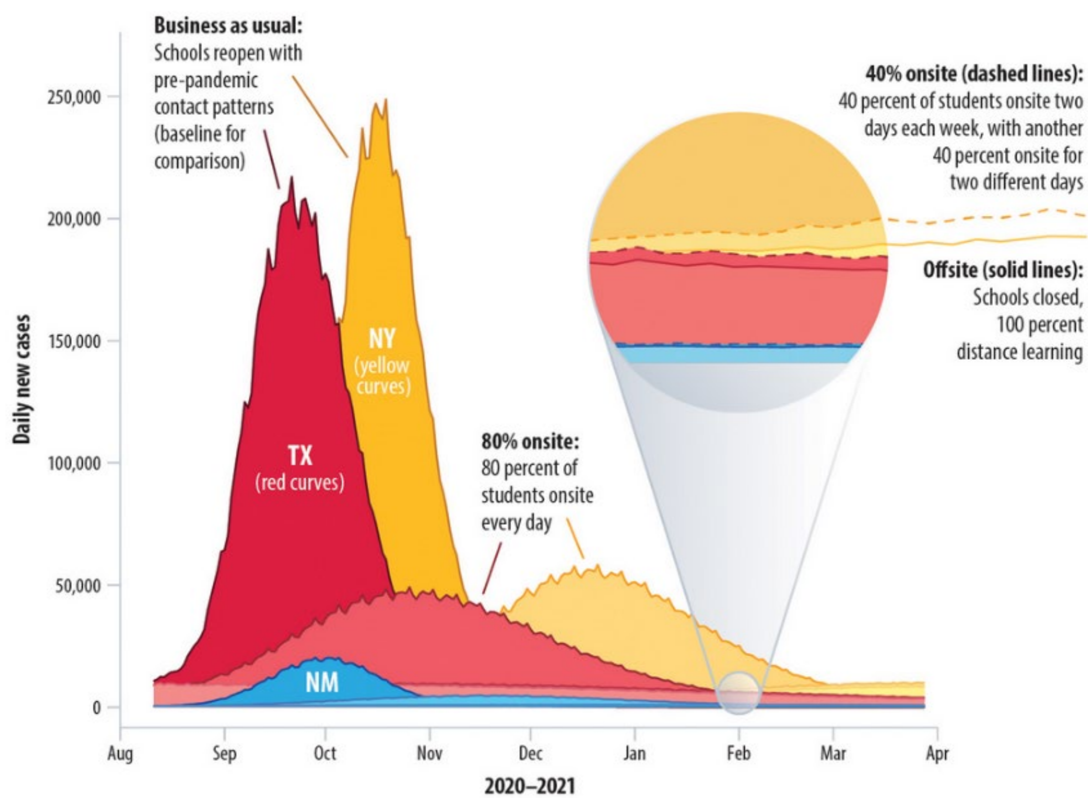


Figure 1: August 2020 projection of case counts in three states (TX, NY, and NM) under four school reopening sceanrios.

Developers imagine a future where epidemiologists use EpiCast in a standing pandemic prevention center, for example in an office within the CDC devoted to identifying and tracking emerging diseases. Armed with EpiCast, the planning and preparation for the next pandemic can begin now. As EpiCast evolves to model populations outside of the United States, researchers will have incredible tools for projecting an outbreak before it happens and learning how best to stop its spread. As a population-modeling tool, EpiCast's applications extend beyond pandemic prevention: EpiCast could be applied to understand other kinds of population behavior, such as in evacuation scenarios.

Compared to other models, EpiCast's advantages are clear. EpiCast simulates disease spread at the much finer census tract level (approximately 2,000 individuals per 65,433 census tracts), compared to the state-level models of competitors. EpiCast can simulate a broad set of mitigation strategies, including industry-specific closures, statewide or county-level isolation, and masking, and a population's varying compliance with these strategies. Its agents are fully characterized individuals, with assigned industries and travel patterns, and potentially even assigned vacations. EpiCast is the best tool to guide school reopenings, as it is the only model to differentiate between high schools and elementary schools when it comes to spread.

In many ways, the United States was woefully unprepared for the COVID-19 pandemic. EpiCast, on the other hand, was always prepared, because developers painstakingly designed it for this precise purpose: guiding the policy that will safely reopen the country.

2. **How does your technology operate?**

EpiCast is a projection model, a sophisticated "agent-based" tool that draws from many independent data sources to run a complex simulation, typically on a high-performance computing platform. In this simulation, EpiCast in effect reproduces the real world, generating millions of individual people ("agents"). Each agent in EpiCast's synthetic population is assigned a set of features such as household location, household composition and size, job category (a North American Industry Classification System, or NAICS, code), and age. We know people behave differently, so instead of creating an "average person" as in an SEIR-type model, EpiCast models individual humans with varying behavior. EpiCast generates a detailed, completely customizable, synthetic population with distinct behaviors and travel patterns.

EpiCast then simulates the individual agents moving throughout their day. Agents go to work, attend school, visit the grocery store, speed to the hospital, or just sit at home all day, all while EpiCast records their interactions and evaluates their exposure to disease. Policymakers want to know what would happen if schools reopened? Researchers need only move that age group from the couch to the classroom, and watch as the scenario plays out in the EpiCast world. The result is a high-resolution, demographic- and locale-specific analysis far ahead of any output from competing models.

Researchers start by inputting individual age- and context-specific contact rates based on the disease's infectivity, incubation period, and mortality. Next, they set a specified number of initially infected people in the population, taking advantage of the model's ability to project results from any starting point. Then, EpiCast simulates 12-hour increments in its generated world, computing the probability of each susceptible individual becoming infected. The model accounts for the duration and closeness of interactions between pairs of individuals in different settings, factoring in a variety of daily patterns. For example, individuals spend the nighttime at home (unless on travel), and daytime at their school or workplace, if they belong to one (and if they are open). When the model shows a susceptible person interacting with an infected person, the susceptible person may become infected, based on a calculated probability. If infected, they enter an incubation period, followed by a symptomatic or asymptomatic phase in which they are infectious, with durations drawn from specified distributions. Infectivity rates, incubation distributions, and other key information are pulled from peer-reviewed literature or derived from trusted data. The pattern repeats and the simulation continues while researchers gather insights as the disease spreads.

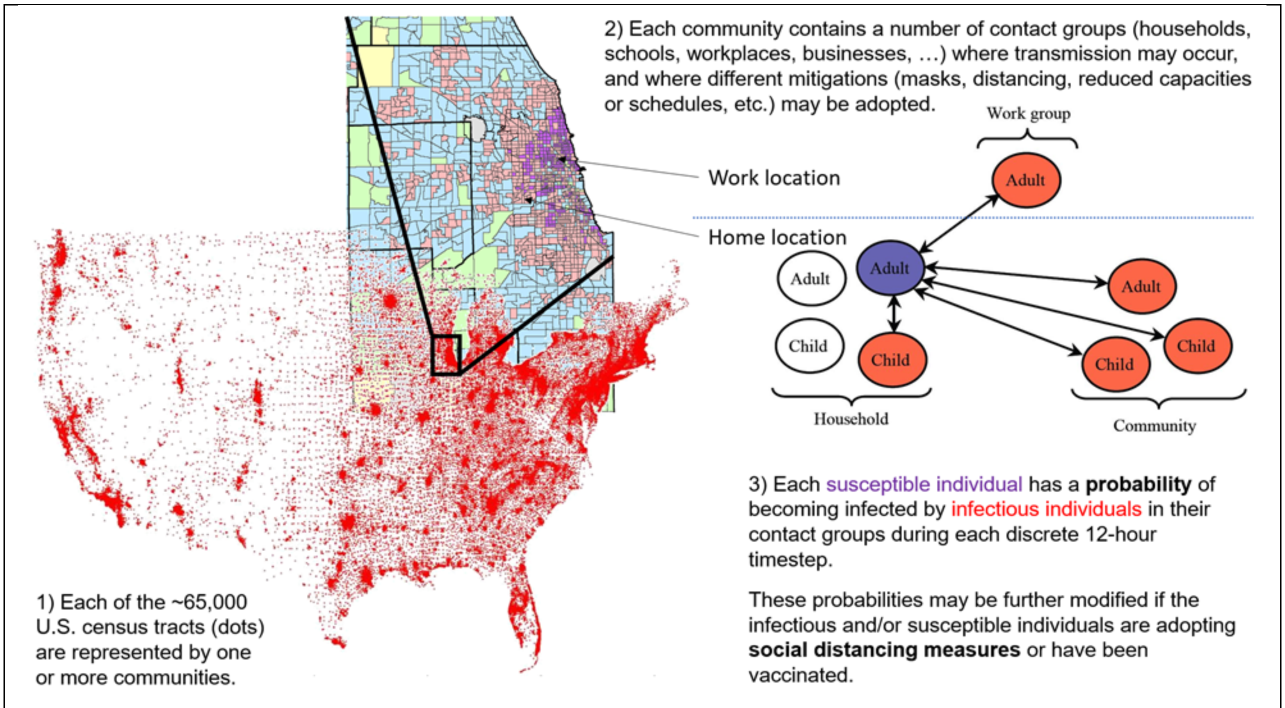


Figure 2: EpiCast uses U.S. census tracts (represented by the red dots on the map) to model population, instead of statewide population data.

Using individual agents to model disease spread provides an extraordinary level of detail. Researchers can evaluate how a disease will ping-pong between restaurant patrons and servers, teachers and students, the socially distant and the not-so-socially distant, tweaking variables and mitigation measures as needed to plot the safest path forward. Researchers can adjust non-pharmaceutical interventions such as social distancing, workplace or school closures, and they can limit the schedules and travel patterns of agents to reflect a local population's adherence to stay-at-home orders. Finally, researchers can determine the best way to introduce vaccines to a population by varying the priority groups (what would happen, for example, if teachers were prioritized for vaccination over first responders). Importantly, researchers can quickly and easily program EpiCast to reflect the increasing infectivity of a disease, say through the discovery of new viral variants.

EpiCast has been used to evaluate numerous public policy scenarios, and school closures are among the most consequential. The figure below, generated by EpiCast and based on national data, shows how offsite learning strategies dramatically curb new infections among school-aged children. From left to right, new infections drop precipitously as a greater share of students shift to offsite learning. The figure indicates that student-student interactions contribute to the majority of new infections across the closure scenarios, up to completely offsite learning. While these policy decisions may never be easy, with EpiCast they can at least be data-driven.

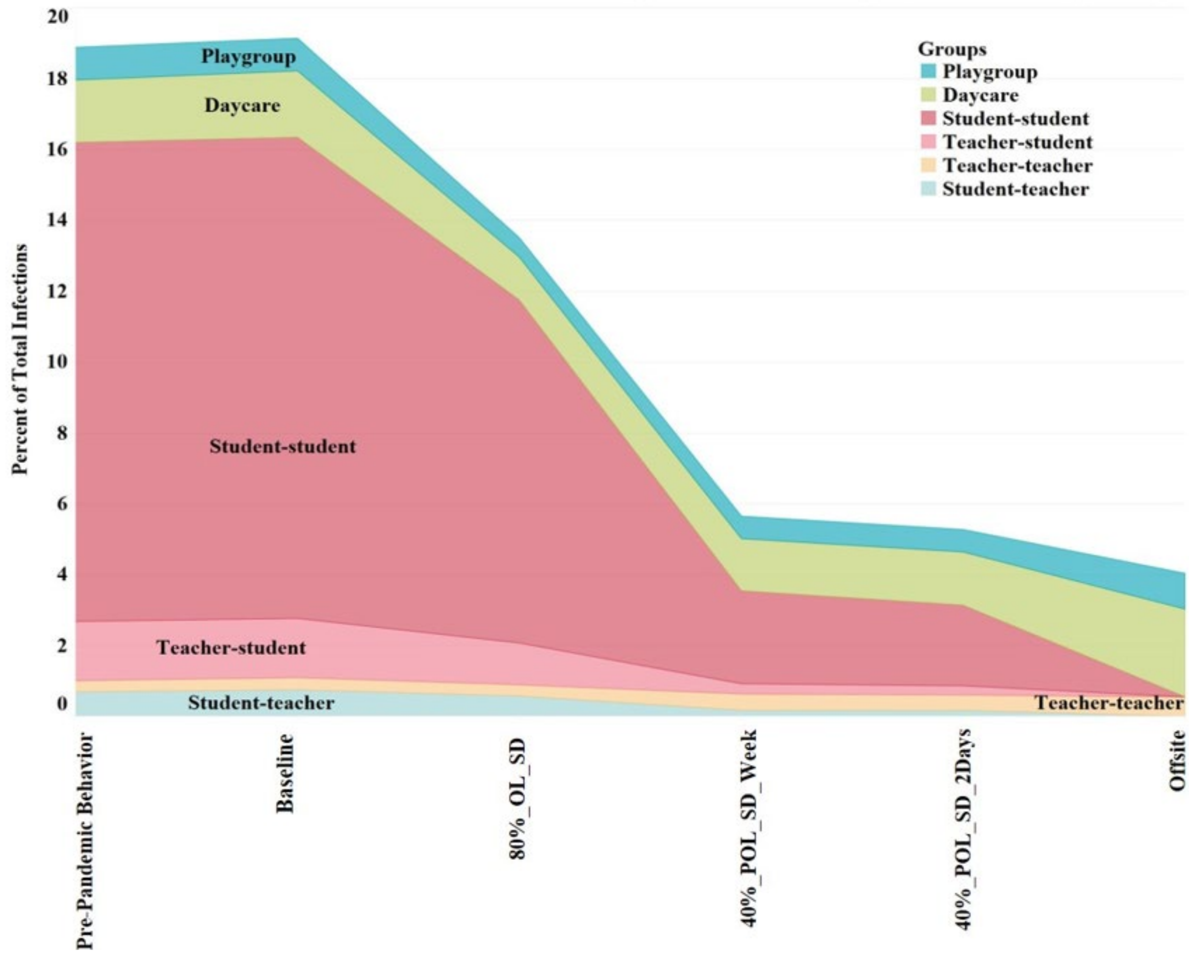


Figure 3: Student-student interactions account for the greatest share of new infections, followed by teacher-student interactions.

For further technical details on how EpiCast works, see the developers' publication in Medrxiv and the article "What Happens Next" in *1663* magazine, both included in the Appendix.

3. Comparison matrix

Imperial College COVID-19 (CovidSim): Agent-based simulation model for the U.S. and U.K. Individuals reside in areas defined by high-resolution population density data. Census data were used to define the age and household distribution size. Within this model, contacts with other individuals in the population are made within the household, at school, in the workplace, and in the wider community. Data on the distribution of workplace size was used to generate workplaces with commuting distance data used to locate workplaces appropriately across the population. However, industry-specific information is not included.

Institute for Health Metrics and Evaluation (IHME): A deterministic SEIR (susceptible, exposed, infectious and recovered) compartmental framework to model the effects of non-pharmaceutical interventions in the United States at the state level. This model does not include the granularity and detail of other agent-based simulations such as schools, industry-specific contact patterns, and age-specific variability in regards to compliance. This model is limited to assessing the impact of social distancing mandates and levels of mask use as well as average mobility, testing, pneumonia seasonality, and others at aggregate and generic population levels.

CoViD19 Modeling Kit (COMOKIT): This agent-based generic framework designed to simulate the spread of disease with high resolution was released in 2020 in response to COVID-19. Although this framework allows users to customize their area of interest and incorporate as much population detail as needed, it does not come with data. Therefore, users need to collect and verify the quality of the data before using it to parametrize the hundreds of parameters available in the model. The model has been validated in Vietnam, but it may require extensive time and effort to adapt it to a different region or disease of interest. This software models populations at the city scale, so it only requires standard computing resources with a graphical user interface.

The Global Epidemic and Mobility Model (GLEAM):

The GLEAM framework is based on a metapopulation approach in which the world is divided into geographical subpopulations. The entire planet is divided into cells with resolution of approximately 25 x 25 kilometers. Subpopulations are constructed from satellite imagery, with each subpopulation centered around a major transportation hub obtained from the International Air Transport Association (IATA) and OAG (a company whose name is derived from its "Official Aviation Guide" origins) database. Hubs generally correspond to major urban areas and airports. A synthetic population is generated using detailed sociodemographic data from publicly available sources, ranging from macro data, such as census data, to micro data, such as surveys on socio demographic features. The framework focuses on population features such as age structure, household composition, school structure, and employment rates. Individuals within these populations are assigned realistic age-specific contact patterns. Individuals can interact in households, schools, workplaces, and the general community. This model relies on air transportation for movement of individuals and does not use ground transportation to capture short-range travel.

<table>
<tr><th>Performance parameter</th><th>EpiCast</th><th>Imperial College</th><th>IHMECensus</th><th>COMOKIT</th><th>GLEAM</th></tr>
<tr><td>Geographic and Spatial Resolution</td><td>United States at the Census tract level</td><td>United Kingdom or United States at the 1x1 kilometer level</td><td>Global, United States at the State level</td><td>Vietnam at the city scale</td><td>Global at the 25x25 kilometers</td></tr>
<tr><td colspan="6">Comments: A model’s geographic and spatial resolution refers to the region and population size it is capable of simulating. EpiCast utilizes census-tract level modeling, allowing for finer granularity in decision-making support. Census tracts generally have a population size between 1,200 and 8,000 people, with an optimum size of 2,000 people. Other models lack this acute resolution, making it difficult to resolve the local effect of proposed changes such as school district reopening.</td></tr>
<tr><td>Workers Stratified by Industry</td><td>Yes</td><td>No</td><td>No</td><td>No</td><td>No</td></tr>
<tr><td colspan="6">Comments: Public health orders responding to COVID-19 restricted industry activities and occupancy limits, for example by shuttering some businesses and limiting occupancy in others. Only EpiCast can model the impact of closures in specific industries, factoring in their distinct exposure levels and risks. This capability is critically important to evaluating a tiered reopening approach.</td></tr>
<tr><td>Intervention strategies proposed by model</td><td>School closures, workplace restrictions by NAICS codes, reduction in contacts due to mask use and social distancing, isolation, and vaccination</td><td>School and university closures, social distancing, quarantine, and case isolation</td><td>Mask use and social distancing</td><td>Travel bans, school closures, social distancing, and case isolation</td><td>Travel restriction, school closures, work from home, social distancing</td></tr>
<tr><td colspan="6">Comments: EpiCast can simulate a much larger variety of “what if” scenarios to inform policy decisions that impact all levels of society.</td></tr>
<tr><td>Heterogeneous social distancing compliance</td><td>Yes</td><td>No</td><td>No</td><td>No</td><td>No</td></tr>
<tr><td colspan="6">Comments: Individuals vary in their enthusiasm for and adoption of preventative social distancing measures. EpiCast accounts for this by using mobility data (cell phone movement) to estimate social distancing compliance in a given area. This provides a better level of detail than competitors because social distancing compliance is a strong determinant of viral spread.</td></tr>
</table>

Performance parameter	EpiCast	Imperial College	IHMECensus	COMOKIT	GLEAM
Able to consider mutations and variants?	Yes	No	No	No	No
Comments: EpiCast can incorporate information about viral variants and differences in infectivity. This capability is important because the multiple circulating strains have different transmissibility and may impact the potential benefit of vaccines and other mitigation measures.					
School Stratification	Yes	No	No	No	No
Comments: EpiCast can discern between school type. This capability is important because student and staff behavior, infectivity, and contact varies based on whether a facility is a high school, elementary school, or preschool. No other models account for this difference.					

4. Describe how your tech outperforms your competitors' tech.

Geographic and spatial resolution. EpiCast models populations at a much finer resolution than competing models. Several competing models use nationwide census data, or at the very finest, statewide data, to create synthetic populations for their projections. EpiCast, on the other hand, leverages population data at the census tract level, so its projections are based on approximately 2,000 person groups instead of entire states. Projections based on these smaller populations are far more effective at simulating the results of policy changes, especially if that policy change is implemented only at a local level.

Stratifies workers by industry. EpiCast is the only model to use North American Industry Classification System (NAICS) codes to assign occupations to its modeled population. This is important because a person's occupation is a key component in evaluating their overall risk of contracting a disease. These industry codes allow policymakers to project the impact of industry-specific closures. For example, EpiCast can model how closing restaurants or the hospitality industry will impact spread. Additionally, this level of granularity enables policymakers to assess the impact of various vaccine distribution approaches (e.g., prioritizing school staff versus prioritizing healthcare workers and first responders).

Capable of modeling diverse intervention strategies. EpiCast is capable of modeling far more intervention strategies than competing models. EpiCast can model school closures, workplace restrictions by NAICS codes, reduction in contacts due to mask use and social distancing, and isolation of cases, both before and after official diagnosis. EpiCast can also model a wide variety of scenarios relating to vaccinations. For example, EpiCast can project the spread of disease if a vaccine is far less effective than predicted, or if a much smaller proportion of the eligible population is vaccinated. EpiCast can even account for differing vaccine hesitancy by county. A sound understanding of these scenarios helps inform public health policy.

Accounts for varying compliance with social distancing. EpiCast successfully leverages cell phone data from UnaCast to reflect real-world social distancing compliance. Compliance with social distancing and travel restrictions varies by county, and EpiCast is able to incorporate this data into its projections.

Incorporates new infectivity information of viral variants. EpiCast was the first model to incorporate the increased infectivity levels of circulating viral variants. Differences in infectivity can drastically impact the course of a disease through a population and impact vaccine effectiveness.

Discerns between school types. Other projection models treat all schools equally in terms of their capability to spread a disease. EpiCast, however, recognizes that high schools and pre-schools present different risks for spread among students and teachers. High school students interact with more people in a given school day, meaning they have a higher chance of interacting with a carrier. Elementary school students, in contrast, interact with fewer students (thus fewer potential carriers), but for a greater duration, meaning that if they do interact with a carrier, their odds of contracting the disease are much higher. These distinctions are important, and they allow EpiCast to more accurately project the outcomes of reopening policies and provide optimal recommendations to when it is safe to reopen.

5. Describe the limitations of your tech.

1. EpiCast is currently parameterized to reflect only the United States. We are pursuing expansion to a global-scale model contingent on accurate census-like data from participating countries. We are collaborating with Brazil to acquire census data for its regions, and have begun the process of coordinating with the World Health Organization (WHO) to facilitate collaborations with other countries.

2. EpiCast currently uses input from the 2000 census because the required tract-to-tract work flow data is not available in the 2010 census. This older data has not greatly impacted the accuracy of our projections because we are able to complement it with more recent data, such as 2020 NAICS codes and cell phone mobility data provided by Unacast in 2020. Epicast will likely benefit from the updated census data once we incorporate it later this year.

3. EpiCast does not explicitly include testing and contact tracing, instead favoring general adjustments to transmission and isolation rates to achieve a similar result. This approach may marginally underestimate the number of asymptomatic or presymptomatic people who are isolating due to contact tracing, but it preserves a massive amount of computing resources while providing comparable information.

4. EpiCast does not automatically include national holidays or other events that may in the short term affect disease spread and case counts. Users must manually adjust the model to account for more frequent travel and higher rates of contact during these periods. The model may be updated to include holidays automatically in the future, but we are currently prioritizing development of other, more important features.

Summary:

For decades, researchers used carefully calculated averages to model infectious disease spread. In this traditional approach, transmission rates dictate the number of “susceptible” individuals that pour into the “infected” bucket, while the “recovered” trickle out. The models’ shortcomings —their weakness in modeling the early and late stages of an outbreak and their inability to account for natural variability in a population—became apparent in March 2020 with the onset of the COVID-19 pandemic. Policymakers needed a better way to understand and predict an uncertain and deadly future while gauging the efficacy of every intervention strategy at their disposal.

The EpiCast disease simulation tool addresses this critical need, empowering policy makers to predict the impacts of an enormous range of variables and mitigation methods, including school and industry-specific closures, social distancing compliance, mask wearing, and vaccinations. No other model evaluates the workforce population by industry classification, enabling priority vaccine distribution to healthcare workers, first responders, and other essential workers. EpiCast stands alone in its unprecedented granularity and fidelity, providing essential information to support public health policy.

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Letters of Support

- Dr. Matthew Biggerstaff, Influenza Division, Centers for Disease Control and Prevention
- Dr. David Scrase, New Mexico Human Services Department
- Dr. Sarah Pallas, World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
and Prevention (CDC)
Atlanta, GA 30341-3724

4/3/2020

Subject: Letter of support for the EpiCast Model for an R&D 100 Award

Dear R&D Award Committee Members:

I am sending this letter to support the nomination of the EpiCast Model for an R&D 100 award. The EpiCast Model is an agent-based simulation of the U.S. that can simulate the spread of diseases, such as COVID-19, and quantify the impact of mitigation strategies.

After novel coronavirus disease was declared a global pandemic, the EpiCast team adapted their model to simulate COVID-19 and subsequently used it to address several critical questions including the assessment of school reopenings, the impact of workplace closures, restrictions, and re-openings, and most recently, the impact of vaccination distribution strategies. As a Co-Lead for the CDC and Interagency Modeling Teams for the COVID-19 response since early 2020, I have been in charge of identifying modeling capabilities that could provide decision support to policy makers and stakeholders. The EpiCast model contributed towards the assessment of several "what if" scenarios to inform COVID-19 planning and development of guidance to mitigate the spread. One of the unique elements of EpiCast is its ability to assess the combined impacts of different interventions in the presence of heterogeneous and emergent behavior. Results from the EpiCast model have helped mitigate the impact of COVID-19 through the development of projections to assist policy decisions and enactment of public health orders.

Capabilities like EpiCast are needed and will be transformative in our ability to understand and respond more effectively to future outbreaks and pandemics. The EpiCast model could be exceptionally useful in providing actionable projections to minimize the potential impact of infectious diseases. Therefore, I am pleased to support the EpiCast Model for the R&D 100 award, as it has great promise for supporting the infectious disease modeling community and in providing decision support to stakeholders.

Sincerely,

Dr. Matthew Biggerstaff
Research Epidemiologist
Applied Research and Modeling Team, Influenza Division, NCIRD
Centers for Disease Control and Prevention

Michelle Lujan Grisham, Governor
David R. Scrase, M.D., Secretary
Angela Medrano, Deputy Secretary
Kari Armijo, Deputy Secretary
Nicole Comeaux, J.D., M.P.H., Medicaid Director

April 1, 2021

Paul J. Heney
VP, Editorial Director
R&D World
1111 Superior Ave., #2600
Cleveland, OH 44114

Dear Mr. Heney,

I write to express my strong support of the nomination of the Los Alamos National Laboratory (LANL) EpiCast Model for a 2021 R&D 100 Award. This model has been critical in providing science-based decision support to assess the impact of COVID-19 mitigation strategies and provide recommendations for New Mexico state pandemic response policies, guidance, and public health orders. As the Secretary of Health and Human Services for the State of New Mexico, I can attest its contributions have had a significant role in the state's COVID-19 response that not only reduced the spread but also save lives.

The EpiCast Team works extensively with me, my staff, and the New Mexico Department of Health so that we could be as informed as possible during the evolving COVID-19 pandemic. This included performing analyses with a short turnaround time, working off-hours, and responding to my numerous texts day and night.

The EpiCast team's expertise was especially important as we wrestled with prediction of the infection rate and how that would strain our limited healthcare resources to respond to and care for New Mexicans. As you may know, New Mexico has a shortage of hospital general beds (17.7) and Intensive Care Unit (ICU) beds (2.2.), lower than the U.S. averages of 23.5 and 2.7 beds per 10,000 residents, respectively. The EpiCast model (an agent-based simulation) provided vital scientific expertise and disease forecasting capabilities to help inform and guide the decisions our office needed to make. Specific areas where their expertise made a positive difference included:

- Highly accurate forecasting of cases, mortality rates, and disease growth rates;
- Modeling for county-by-county prediction of disease transmissibility;
- Modeling school reopening scenarios;
- Detailed tracking and forecasting of hospital and ICU bed utilization;
- Providing behavioral health utilization analyses;
- Anticipation and forecasting of the need for additional shelter capacity; and,
- Prediction of vaccination impacts.

I know the talents of the EpiCast team during the COVID-19 pandemic were only available because of many prior years of sustained and dedicated scientific research and development at LANL. LANL

HUMAN SERVICES DEPARTMENT

Michelle Lujan Grisham, Governor
David R. Scrase, M.D., Secretary
Angela Medrano, Deputy Secretary
Kari Armijo, Deputy Secretary
Nicole Comeaux, J.D., M.P.H., Medicaid Director

embodies the kind of scientific leadership that is so important for our state and for the United State. It has been such an honor and privilege to work for a Governor who is evidence based and science oriented, to the point of requiring the development of some of the nation's best COVID data systems here in New Mexico. The team at LANL is a major factor to our success, and it makes me proud that New Mexico is home to such scientific leadership. I wholeheartedly support the nomination of the EpiCast team for a 2021 R&D 100 Award.

Sincerely,

David R. Scrase, M.D.
Cabinet Secretary
New Mexico Human Services Department

Office of the Secretary|PO Box 2348 – Santa Fe, NM 87504|Phone: (505) 827-7750 Fax: (505) 827-6286

April 7, 2021

Subject: Letter of support for the EpiCast Model for an R&D 100 Award

Dear R&D Award Selection Committee Members:

I am delighted to lend my support to the nomination of the EpiCast Model for an R&D 100 award. The EpiCast Model is an agent-based simulation of the U.S. used to simulate the spread of diseases, such as COVID-19, as well as to understand and measure the potential impact of "what if" mitigation strategies. After the novel coronavirus disease (COVID-19) was declared a global pandemic in early March 2020, the EpiCast team adapted their model to simulate COVID-19 and assess the impact of non-pharmaceutical (e.g., facemask, closures, isolation) and pharmaceutical (e.g., vaccines) intervention strategies.

I am a member of the World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE) Working Group on COVID-19 Vaccines, which has as part of its terms of reference to "provide guidance for the development of prediction models to determine the optimal age groups and target populations for vaccine introduction and guide vaccine introduction for optimal impact." The EpiCast team provided reports and briefings on their vaccine distribution modeling scenarios to the WHO SAGE Working Group on COVID-19 Vaccines. In particular, the EpiCast model explored the impact of vaccination strategies in school settings, the only model identified at that time for such settings, which was important in considering vaccination prioritization strategy options for teachers and school staff, as well as interactions between vaccination prioritization approaches and school-based mitigation measures.

Models like EpiCast have played a significant role in the nation's and the world's COVID-19 response and are critical for responding to future disease outbreaks and pandemics. I strongly support the EpiCast Model for the R&D 100 award, given its demonstrated value in providing decision support to diverse stakeholders responding to infectious disease threats and its potential for further development for future policy and programmatic applications.

Sincerely,

Dr. Sarah Pallas
Economist
Global Immunization Division
U.S. Centers for Disease Control and Prevention
1600 Clifton Road NE
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Email: spallas@cdc.gov

Appendix List

- “Using an Agent-Based Model to Assess K-12 School Reopenings Under Different COVID-19 Spread Scenarios – United States, School Year 2020/21” Timothy C. Germann et al., *Medrxiv*, October 2020
- “What Happens Next” Craig Tyler, *1663*, February 2021
- “At Los Alamos National Lab, Supercomputers Are Optimizing Vaccine Distribution” Oliver Peckham, *HPC Wire*, December 17, 2020
- “Distributing a highly anticipated new release: The COVID-19 vaccine” Los Alamos National Laboratory Press Release, LA-UR-20-30256, December 16, 2020
- “COVID-19 Vaccine Critical But It’s Not Silver Bullet” Sara Del Valle and Ben McMahon, *Santa Fe New Mexican*, January 5, 2021
- “Assessing The Impact of Vaccine Distribution Strategies Using an Agent-Based Model” Timothy Germann et al., WHO SAGE Working Group on COVID-19 Vaccines, LA-UR-20-3071
- “School dismissal as a pandemic influenza response: When, where and for how long?” Timothy Germann et al., *Epidemics*, June 2019

Using an Agent-Based Model to Assess K-12 School Reopenings Under Different COVID-19 Spread Scenarios – United States, School Year 2020/21

Timothy C. Germann[1], Manhong Z. Smith[2,3], Lori Dauelsberg[2], Geoffrey Fairchild[2], Terece L. Turton[4], Morgan E. Gorris[2,3], Chrysm Watson Ross[2,5], James P. Ahrens[6], Daniel D. Hemphill[7], Carrie Manore[2], and Sara Y. Del Valle[2*]

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Abstract

School-age children play a key role in the spread of airborne viruses like influenza due to the prolonged and close contacts they have in school settings. As a result, school closures and other non-pharmaceutical interventions were recommended as the first line of defense in response to the novel coronavirus pandemic (COVID-19). Assessing school reopening scenarios is a priority for states, administrators, parents, and children in order to balance educational disparities and negative population impacts of COVID-19. To address this challenge, we used an agent-based model that simulates communities across the United States including daycares, primary, and secondary schools to quantify the relative health outcomes of reopening schools. We explored different reopening scenarios including remote learning, in-person school, and several hybrid options that stratify the student population into cohorts (also referred to as split cohort) in order to reduce exposure and disease spread. In addition, we assessed the combined impact of reduced in-person attendance in workplaces (e.g., through differing degrees of reliance on telework and/or temporary workplace closings) and school reopening scenarios to quantify the potential impact of additional transmission pathways contributing to COVID-19 spread. Scenarios where split cohorts of students return to school in non-overlapping formats resulted in significant decreases in the clinical attack rate (i.e., the percentage of symptomatic

individuals), potentially by as much as 75% . These split cohort scenarios have impacts which are only modestly lesser than the most impactful 100% distance learning scenario. Split cohort scenarios can also significantly avert the number of cases–approximately 60M and 28M–depending on the scenario, at the national scale over the simulated eight-month period. We found the results of our simulations to be highly dependent on the number of workplaces assumed to be open for in-person business, as well as the initial level of COVID-19 incidence within the simulated community. Our results show that reducing the number of students attending school leads to better health outcomes, and the split cohort option enables part-time in-classroom education while substantially reducing risk. The results of this study can support decisions regarding optimal school reopening strategies that at the population level balance education and the negative health outcomes of COVID-19.

Disclaimer:

This work was sponsored by the United States Centers for Disease Control and Prevention. Los Alamos National Laboratory, an affirmative action/equal opportunity employer, is operated by Triad National Security, LLC, for the National Nuclear Security Administration of the United States Department of Energy under contract # 19FED1916814CKC. Approved for public release: LA-UR-20-27982.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or Los Alamos National Laboratory.

1. Introduction

The novel coronavirus disease (COVID-19) was first identified in Wuhan, China in late December 2019 [3] and subsequently spread worldwide. By March 11, 2020, when the World Health Organization (WHO) declared COVID-19 as a global pandemic, there were already close to 120,000 confirmed cases and more than 4,300 deaths worldwide [4]. As of October 8, 2020, there are now over 36 million confirmed cases and over a million deaths worldwide, with over 7.8 million confirmed cases and over 217,000 deaths in the U.S. [5]. The COVID-19 virus spreads primarily through small droplets and aerosols of saliva or discharge from the nose of an infected person [6]. At this time, there are no specific vaccines or large-scale treatments for COVID-19 [6], demonstrating the urgent need for non-pharmaceutical approaches that could reduce its spread.

Public officials have recommended a range of individual- and community-level non-pharmaceutical interventions to slow the spread of COVID-19 and mitigate the impact on people, communities, and healthcare infrastructure [7]. Individual measures include personal protective actions, such as applying proper cough etiquette in daily life, hand hygiene, wearing face coverings/masks, staying home when sick (also called isolation), or staying home after an exposure to a confirmed case or after residing in/arriving from a community with known widespread transmission (also called quarantine). Community measures may include temporary school closures/dismissals and other social distancing measures such as stay-at-home recommendations, canceling mass gatherings, and minimizing face-to-face contact at workplaces.

As the cases of COVID-19 started to emerge during the early spring of 2020 in the U.S., most of the primary and secondary schools closed for the remainder of the 2019-2020 school year [8]. There has been a significant debate about school closures and reopenings because of the existing educational disparities that have been exacerbated by the pandemic, social isolation, and other unintended consequences such as access to free and subsidized lunches at school. However, there is anecdotal evidence that reopening schools, for the traditional academic year in autumn 2020, in areas experiencing widespread community transmission provide additional transmission pathways between communities that were otherwise mostly isolated. For example, the Cherokee County School District in Georgia reported 108 confirmed cases of COVID-19 within two weeks of schools reopening, and 3 out of the 6 high schools in the district reverted to full remote leaning by the third week [9, 10]. In Mississippi, 71 of the 82 counties reported positive COVID-19 cases within few weeks of schools reopening [11]. Similarly, in Tennessee, over 2,000 children tested positive for COVID-19 within two weeks of schools reopening [12].

Mathematical and computational models of COVID-19 spread provide a platform to examine which modalities of in-person instruction may be feasible during the ongoing COVID-19 pandemic. Several recent studies have begun to quantify the impact of various non-pharmaceutical interventions in combination with different school reopening strategies and have found that reopening schools as normal is likely to increase the number of COVID-19 cases [13, 14]. Other studies have found that closing schools and incorporating social distancing measures in classrooms are effective in reducing the spread of COVID-19 [15]. In addition, hybrid approaches to learning, such as capping the in-person classroom size, may be effective in reducing transmission [14,16] and provide a balance approach between supporting education while limiting the spread of COVID-19.

An additional challenge of simulating the impacts of COVID-19 within a community is also simulating workplace restrictions, which may reduce transmission pathways within the community. We address this gap by combining non-pharmaceutical interventions, school reopening scenarios, and workplace restrictions into an agent-based model, EpiCast, to assess the potential feedbacks on the spread of COVID-19. Using parameters provided by the Centers for Disease Control and Prevention (CDC) to simulate COVID-19 transmission within the U.S., we explored several reopening scenarios including remote learning, in-person school, and several hybrid options that stratify the student population into cohorts in order to reduce exposure and disease spread. The results of this study can support decisions regarding optimal school reopening strategies that balance education and the negative health outcomes of COVID-19.

2. Methods

Model Description

We used an agent-based model, known as Epidemiological Forecasting (EpiCast), originally designed to simulate community-level influenza transmission in the U.S. at the national-scale and adapted it to simulate COVID-19 [17]. The primary modifications for COVID-19 relate to the disease natural history (as described later) since the transmission mechanisms for COVID-19 are similar to that for influenza. The national-scale simulation model consists of 281 million individuals distributed among 65,334 census tracts to closely represent the actual population distribution according to the 2000 U.S. Census data [17]. Each tract is organized into 2,000-person communities resulting in 180,492 model communities. The model combines U.S. Census demographics and worker-flow data to generate daytime and evening contact networks based on potential contacts emerging at daycares, schools, workplaces, households, neighborhoods (~500 people), and communities (e.g., mall, supermarket) [17]. In each census tract, the synthetic population matches the actual population in several statistical measures including the number of residents and households, the household's age distribution, the household size and membership distribution, and employment status for working adults. In addition, each workplace is assigned a 3-digit NAICS (North American Industrial Classification System) code based on the proportion of workers in each sector in each county. We used a regional model (~8.6 million people in the Chicago Metropolitan Statistical Area (MSA)) to explore additional scenarios (given the extensive computational nature of the national model) in order to determine the impact of different assumptions on COVID-19 spread and mitigation strategies.

A new feature of EpiCast, for the purpose of this study, is the ability to capture interactions between teachers and students while in school settings. In previous EpiCast simulation models [17,18], school mixing groups accounted only for transmission between students; teachers and staff were not explicitly included. For the present study, we associate a workplace with NAICS Subsector Code 611

(Educational Services) with each school, and account for mixing between the teachers, staff, and school children. Where necessary, we add additional workplace(s) in a community to achieve an average 14:1 student:(teacher/staff) ratio in each school, based on recent statistics from the National Center for Education Statistics [19]. This is necessary because our community model assumes that elementary and secondary school children attend school in the tract/community in which they reside, not accounting for bussing across Census tract boundaries which the actual employment statistics reflect. Transmission between children in a school mixing group, and between teachers/staff in a workplace mixing group, are unchanged from the original model. For the added mixing, from students to teachers/staff and vice versa, we assume that the individual child-adult contacts are twice the child-child contact rates. Our results were not overly sensitive to this assumption, and we note that the numbers of child-child transmissions are still greater than child-adult transmission due to the much larger number of children in a school. For example, if there are approximately 14 times more children than adults in a school, and approximately two times greater transmission between an individual child and individual adult, the child-child transmission will be about seven times greater than child-adult transmission.

Epidemiological Parameter Assumptions

In order to simulate COVID-19 transmission within a community, we used parameter assumptions and model-produced epidemiological data from the CDC's Pandemic Planning Scenarios [20] (Table 1). The disease natural history for COVID-19 was assumed to be as follows: the distribution of latent infection is 1-7 days, the incubation period is 1-8 days, and infectious period is 3-9 days. Furthermore, the proportion of infections which remain asymptomatic are assumed to be 40% and the relative infectiousness of asymptomatic or pre-symptomatic individuals is assumed to be 75%. Self-isolation of symptomatic individuals is assumed to be similar to those used for pandemic influenza studies [21]. Assumptions regarding ideal reduction in contacts due to social distancing, facemasks, and hygiene is shown in Table 2. The "reduced" social distancing scenarios assume a 50% reduction in compliance of preschool and elementary school-age children to account for limited facemask or social distancing measures. Finally, long distance travel is assumed to be reduced due to travel and quarantine restrictions implemented across the nation (Table 2). Each county was initialized and calibrated to match the cumulative case counts during the first two weeks of August 2020 as reported by the New York Times COVID-19 repository [22]. Note that we do not report the number of cases during the calibration phase and thus assume that the simulation starts on August 15, 2020.

Table 1. Summary of Key EpiCast model parameters for this study.

Parameter	Age Group			
	0-49	50-64	65+	Overall
Symptomatic case hospitalization rate	0.017	0.045	0.074	0.034
Symptomatic case fatality rate	0.0005	0.002	0.013	0.004

Percentage of hospitalized cases requiring treatment in the ICU	23.6%	36.2%	35.1%	-
Percentage of hospitalized cases requiring >= 1 day of ventilator use	11.7%	21.8%	21.3%	-

Assumptions regarding full time, part-time, the number of individuals teleworking, and employees laid off as a result of the current COVID-19 situation are shown in Table 2. Some of these percentages were chosen based on discussions with subject matter experts from the State of New Mexico. Furthermore, the percentage of individuals teleworking are based on two surveys of the labor market near the beginning of the COVID-19 pandemic in the U.S. from the Bureau of Labor Statistics (BLS) [23]. The ability to telework for each 3-digit NAICS sector also comes from the BLS survey and is shown in Table 3. The model assumptions on working in the workplace versus working from home or being laid off were based on the values in both Table 2 and Table 3.

Table 2. Workforce status & reduction in contacts due to social distancing assumptions.

	Working Status				Reduction in Contacts due to social Distancing		Long Distance Travel
Workplace Assumption	**Full Time**	**Part-time or Shift**	**Telework Take-up**	**Laid Off**	**Workplace**	**Other non-household**	
Fewer Open Workplaces	44%	32%	20%	16%	10%	50%	50%
More Open Workplaces	52%	32%	15%	8%	10%	25%	75%

Table 3. Ability to Telework by NAICS 2-Digit Sector.‡

NAICS Sector	NAICS 2-Digit Code	Ability to Telework (Median)
Agriculture & Mining	11	8.1%
Utilities & Construction	21-23	32.7%
Manufacturing	31-33	41.0%
Wholesale	42	26.5%
Retail	44-45	26.5%
Transportation & Warehousing	48-49	32.7%
Information	51-52	80.4%
Finance, Insurance, & Real Estate	52-53	81.1%
Professional and Business Services	54-56	71.6%

Education	61	47.9%
Health & Social Services	62	47.9%
Leisure & Hospitality	71-72	20.3%
Other Services	81	39.9%
Government & Administration	92	57.0%

‡The information from BLS is by 3-digit NAICS sector (and is used in the model at the 3-digit level) but is shown as 2-digit for brevity as most 3-digit levels share the same value as those in the rolled-up 2-digit NAICS category.

Workplace Modeling Assumptions

Per the phase guidelines released in Opening Up America Again [24], we modeled two scenarios: "Fewer Open Workplaces," similar to Phase 2 of Opening Up America Again, and "More Open Workplaces", similar to Phase 3. These two scenarios describe different levels of in-person workplace assumptions (Figure 1, Tables 2-3). Specifically, Fewer Open Workplaces encourages telework whenever possible and feasible with business operations as well as limited onsite operations for a small set of businesses. More Open Workplaces assumes staffing of additional worksites with an expanded number of onsite workers. An example is a retail business may be open to 25% customer capacity as per Phase 2 recommendations and the NAICS industry percentage of employees working onsite is 50% (in order to accommodate the workers necessary for the operation of the business) for Fewer Open Workplaces. For More Open Workplaces, this business may have the opportunity to have a 50% customer capacity and the percentage of employees needed would increase to 75%. For a comparison across intervention approaches, we also use a Pre-pandemic Behavior scenario, which assumes that all businesses are open with no capacity or social distancing restrictions.

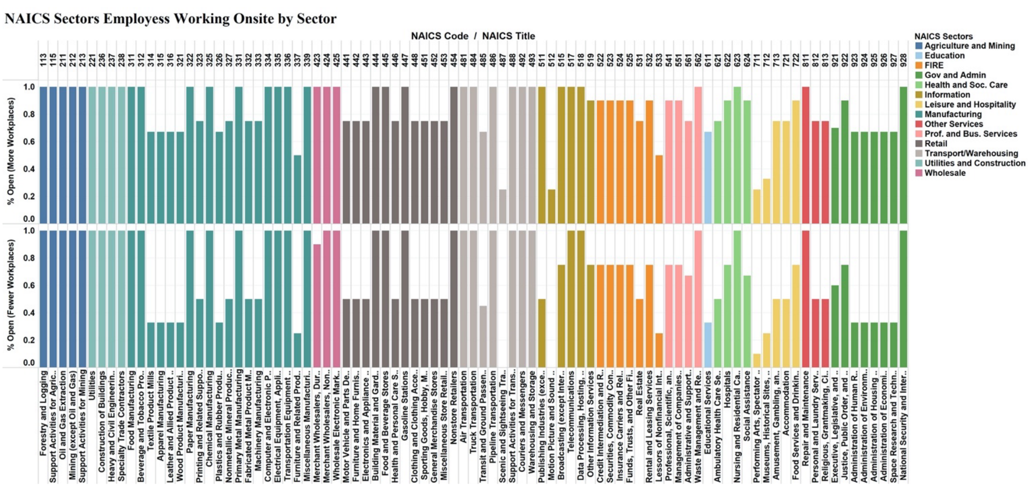

Figure 1. NAICS sectors assumptions for Fewer Open Workplaces and More Open Workplaces.

School Scenarios

We explored the impact of various school reopening scenarios as described in Table 4. These scenarios range from 100% distance learning to 100% onsite learning (Baseline), as well as partial onsite learning with alternating days or weeks. We also explored 80% in-person enrollment due to recent surveys, which suggest that at least 20% of parents may not send their children back to school [25]. For the regional model, we assume that the 2020-2021 school year for the Chicago Public Schools begins on September 8th, 2020. The national scale model assumes a different start date for the 2020-2021 school year ranging from August 3rd, 2020 (Arizona) to September 16th, 2020 (New York) based on publicly available information from school districts.

Table 4. Descriptions of school reopening, baseline, and pre-pandemic scenarios.§

Scenario Name	Scenario Code	Scenario Description
Pre-Pandemic Behavior	Pre-Pandemic Behavior	No mitigations, all businesses completely open (i.e., 100% enrollment with no social distancing in place).
Baseline	Baseline	All students physically in school with some social distancing (i.e., 100% enrollment).
80% Onsite Learning with **Reduced** Social Distancing‡	80%_OL_LessSD	All enrolled* students physically in school.
80% Onsite Learning with **Ideal** Social Distancing†	80%_OL_SD	All enrolled* students physically in school.
80% Partial Onsite Learning – **Alternating Week** with **Reduced** Social Distancing‡	40%_POL_LessSD_Week	Two non-overlapping cohorts of students – 40% of the students attend one week and the other 40% attend the next week.
80% Partial Onsite Learning – **Alternating Days** with **Reduced** Social Distancing‡	40%_POL_LessSD_2Day	Two non-overlapping cohorts of students – 40% of the students attend for two days/week (Mon/Tue) and the other 40% attend for two days (Thu/Fri). Wednesday off for disinfection.
80% Partial Onsite Learning – **Alternating Weeks** with **Ideal** Social Distancing†	40%_POL_SD_Week	Two non-overlapping cohorts of students – 40% of the students attend one week and the other 40% attend the next week.
80% Partial Onsite Learning – **Alternating Days** with **Ideal** Social Distancing†	40%_POL_SD_2Days	Two non-overlapping cohorts of students – 40% of the students attend for two days/week (Mon/Tue) and the other 40% attend for two days (Thu/Fri). Wednesday off for disinfection.
100% Distance Learning	Offsite	No students physically in school.

§Note that given the similar results between all the "Less SD" scenarios in the regional simulations, we did not run the Less SD for the nationwide scenarios.
*Note that 80% in-person enrollment was used due to recent surveys that suggest that at least 20% of parents may not send their children back to school [25].
† *Ideal social distancing* assumes 50% reduction in contacts due to students staying 6 ft from other people, increased hygiene, and masks/face coverings.
‡ *Reduced social distancing* assumes 25% reduction in contacts of preschool and elementary school-age children to account for limited facemask use or limited social distancing measures.

3. Results

Overall Regional and National Impacts

The impacts of school reopening for the Chicago MSA region are summarized in Figure 2 and Tables A-1 and A-2 in the Appendix. Figure 2 shows the epidemic curves for nine school reopening scenarios under Fewer Open Workplaces and More Open Workplaces for the Chicago MSA region aggregated over the simulated eight-month period (15 August 2020 through 11 April 2021). Figure 3 shows the national simulation results of six scenarios under Fewer Open Workplaces and More Open Workplaces for the nation. The results show similar trends for the Baseline, 80% in-person learning, 40% 2-day and alternating week, and offsite school scenarios with Fewer Open Workplaces and More Open Workplaces assumptions for both regional and national simulations.

All the partial onsite learning scenarios delay the epidemic peak and flatten the curve for Fewer Open Workplaces, which is consistent with previous studies on school closures [13-16] (Figure 2, 3). However, for More Open Workplaces, the peak for most scenarios is spread around three weeks regardless of school reopening scenario and the impact of hybrid school reopenings is reduced. Additionally, the reduced social distancing scenario (analyzed only the Chicago MSA region), which accounts for limited compliance in facemask usage and social distancing measures for children in K-8 (i.e., kindergarten through grade 8th), has a slight but significant decrease in the clinical attack rate (CAR) (i.e., the percentage of symptomatic individuals) over the simulated eight-month period. That is, for the Fewer Open Workplaces scenario, the CAR is reduced from 26.3% for the 80% less social distancing scenario to 23.8% for the ideal social distancing scenario. Similarly, the CAR is reduced for the 40% 2-day split cohort scenario from 8.8% to 5.8% for the Fewer Open Workplaces scenarios depending on the ideal or reduced social distancing assumptions, respectively. These results show that reducing the number of students attending in-person education as well as splitting the student population into cohorts, can reduce the potential negative impacts of COVID-19 spread.

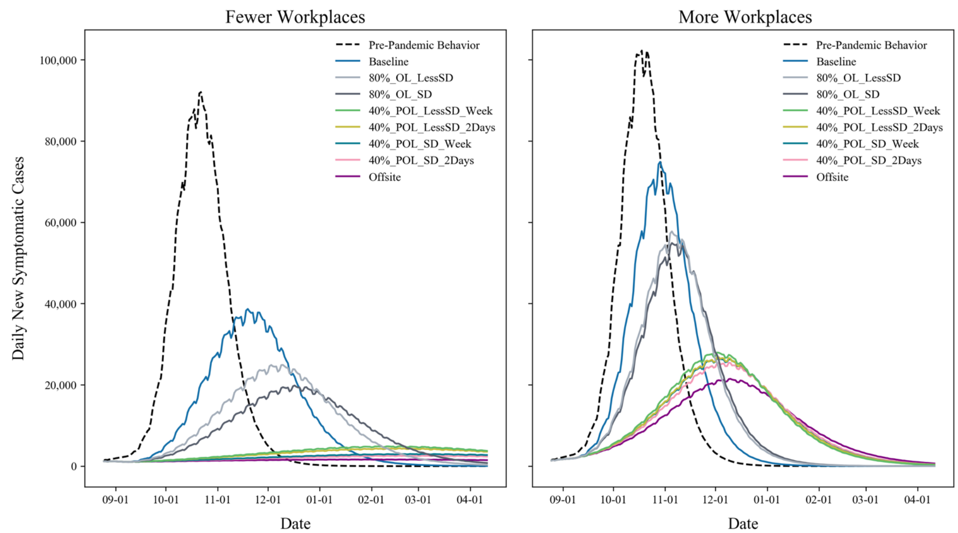

Figure 2. Chicago MSA results from the EpiCast model for various school opening scenarios under Fewer Open Workplaces and More Open Workplaces.

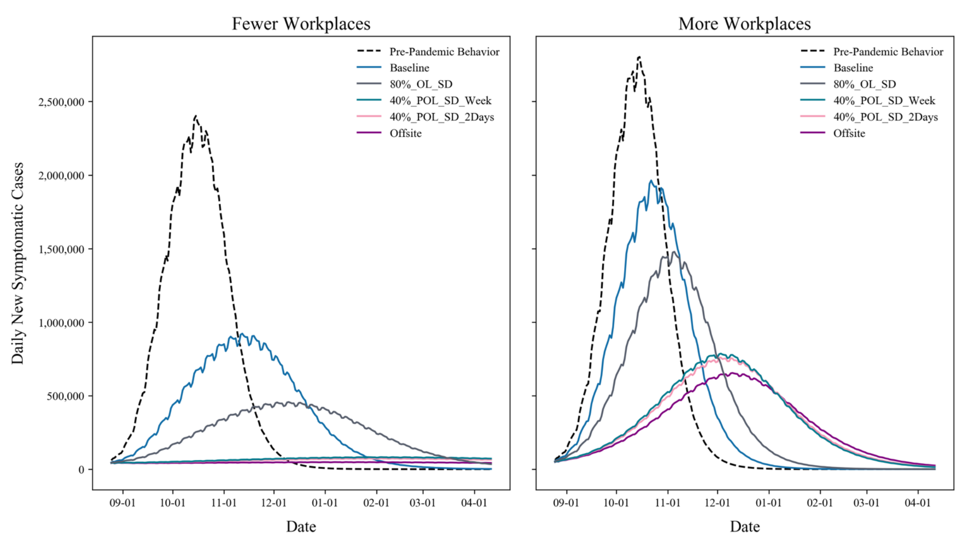

Figure 3. National results from the EpiCast model for various school opening scenarios under Fewer Open Workplaces and More Open Workplaces.

The results show heterogeneity in the impacts across the U.S. Figures 4-5 show cumulative cases per 100K population at the county level for EpiCast simulated results for the 40% split cohort scenario attending 2 days a week and the 80% onsite school scenario. Note that the cumulative number of cases include both symptomatic and asymptomatic individuals aggregated over eight-months.

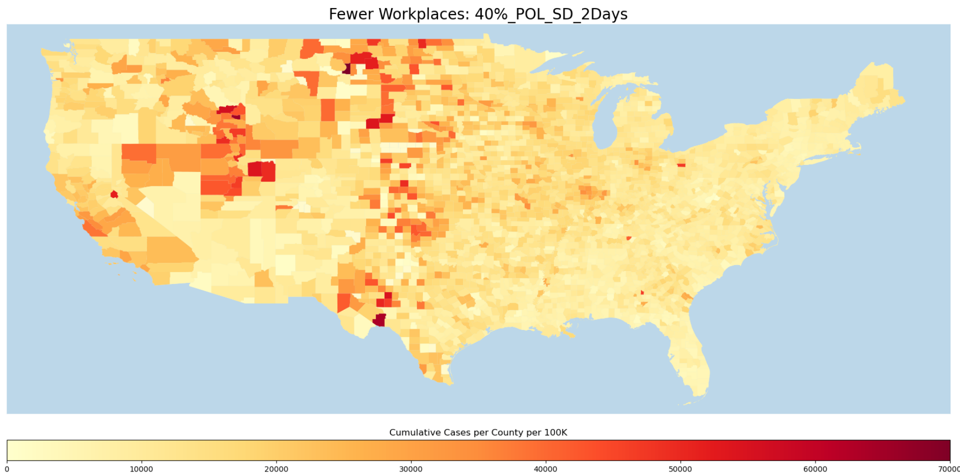

Figure 4. Cumulative cases per county per 100K for EpiCast simulated results for two non-overlapping cohorts of 40% of students attending school 2-days a week.

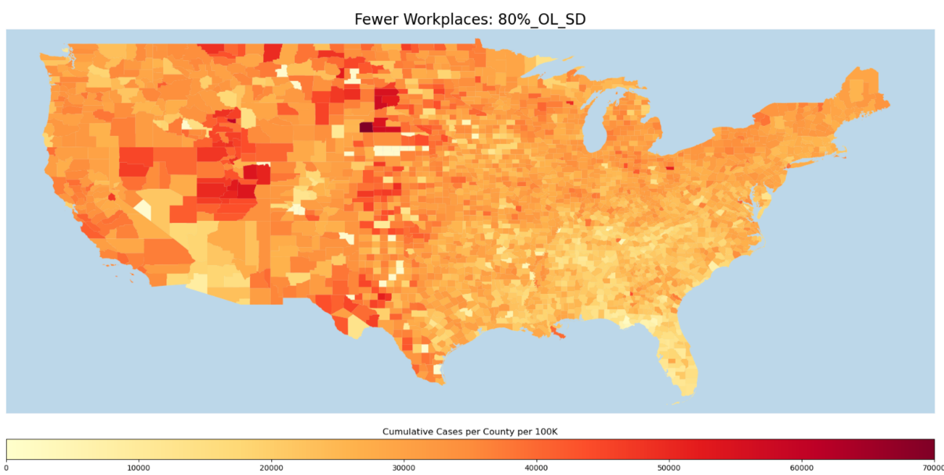

Figure 5. Cumulative cases per county per 100K for EpiCast simulated results for 80% of students attending school full time.

Tables 5-6 show key results from the model aggregated for the nation. Table 5 shows the total number of cases, deaths, and hospitalizations for each scenario for the full eight-month simulation period and for the four weeks around the peak of the epidemic. Table 6 shows the peak incidence and prevalence as well as the time to peak and the total CAR for each scenario. Note that the cumulative number of cases includes both symptomatic and asymptomatic individuals as simulated by EpiCast. Similar impacts as the Chicago MSA model (see Appendix) are observed at the national level but the overall attack rate is lower for all scenarios. Specifically, the scenarios with the lowest attack rate include the 100% offsite, 40% 2-day and alternating weeks school scenarios (i.e., Fewer Open Workplaces: 4.1%, 5.6%, and 6.1%, respectively). As noted earlier, the impacts of COVID-19 spread is lower for the Fewer Open Workplaces compared to the More Open Workplaces for all scenarios.

Table 5. Summary of key EpiCast results for the Nation – Part 1

Workplace Assumptions	Scenario Name	During Peak 4 Weeks			August 15, 2020 to April 11, 2021		
		Cases	Hospitalized	Deaths	Case	Hospitalized	Deaths
Fewer Open Workplaces	Pre-Pandemic Behavior	59,664,577	1,798,188	107,322	110,244,127	3,370,360	230,451
	Baseline	24,323,551	685,746	38,649	75,049,776	2,132,798	128,292
	80%_OL_SD	12,346,146	354,878	20,900	55,178,391	1,588,821	95,848
	40%_POL_SD_Week	2,263,045	67,090	4,108	15,922,257	466,195	27,874
	40%_POL_SD_2Days	1,997,647	59,056	3,624	14,457,662	424,601	25,474
	Offsite	1,336,844	39,827	2,484	10,665,240	316,245	19,169
More Open Workplaces	Pre-Pandemic Behavior	68,242,756	2,064,544	120,162	116,608,169	3,584,053	242,236
	Baseline	49,681,358	1,470,601	84,679	102,532,010	3,071,051	198,517
	80%_OL_SD	38,469,699	1,156,296	69,342	93,355,312	2,830,004	184,520
	40%_POL_SD_Week	21,206,204	657,099	42,085	75,101,132	2,331,432	154,298
	40%_POL_SD_2Days	20,479,987	636,866	41,009	73,871,330	2,296,792	152,097
	Offsite	17,756,292	556,366	36,073	68,375,029	2,139,919	142,522

Table 6. Summary of key EpiCast results for the Nation – Part 2

Workplace Assumptions	Scenario Name	Peak Incidence (Cases per 1000)	Time to Peak Incidence (days)	Peak Prevalence (Cases per 1000)	Time to Peak Prevalence (days)	Clinical Attack Rate (%)
Fewer Open Workplaces	Pre-Pandemic Behavior	2,402,432	62	51	66	42.4
	Baseline	922,097	90	19	94	28.9
	80%_OL_SD	456,896	118	10	122	21.2

	40%_POL_SD_Week	82,209	174	2	178	6.1
	40%_POL_SD_2Days	72,686	174	2	178	5.6
	Offsite	50,110	8	1	157	4.1
More Open Workplaces	**Pre-Pandemic Behavior**	2,803,605	62	59	65	44.8
	Baseline	1,963,443	69	41	73	39.4
	80%_OL_SD	1,478,282	83	31	87	35.9
	40%_POL_SD_Week	786,216	111	17	115	28.9
	40%_POL_SD_2Days	758,840	111	16	115	28.4
	Offsite	654,784	118	14	122	26.3

Source of Infection

Identifying the source of infection can help develop targeted mitigations to reduce the potential spread of viruses. Figure 6 shows the source of infection for all the national-level scenarios for Fewer Open and More Open Workplaces for all contact settings within the simulation. Our results show that the majority of cases are generated at home, followed by neighborhood/community settings. The percentage of infection generated in schools and workplaces is correlated with the level of schools/workplaces open. Note that additional infections generated at workplaces are captured under neighborhood/community due to the fact that EpiCast does not explicitly account for customer interactions with workers at workplaces/workgroups. Workgroups only account for infections generated from employee to employee. Figure 7 shows the aggregated source of infection for daycares, playgroups, and schools for all the national-level scenarios for Fewer Open and More Open Workplaces. Note that the majority of school-related infections are generated from student-student interactions due to the prolonged close contacts in these settings. This finding supports strategies that reduce the number of students attending in-person education.

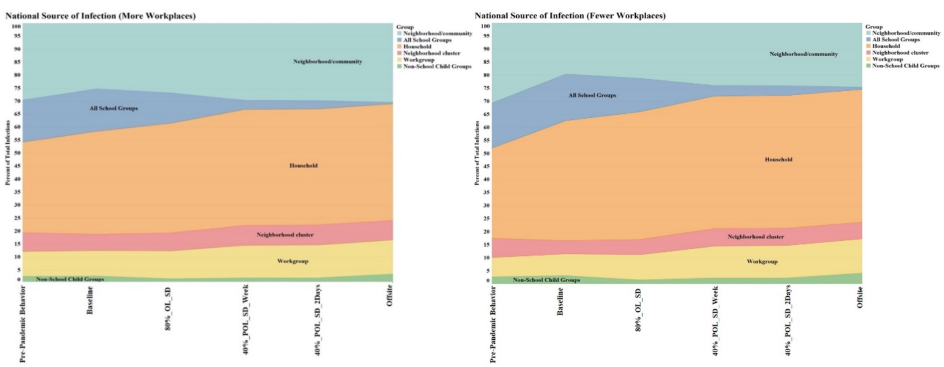

Figure 6. Source of infection for each of the national-level scenarios for Fewer Open and More Open Workplaces. Note that about 30% of the infections are generated at home, 20% at neighborhood/community settings, 15% at schools, and 10% at workplaces.

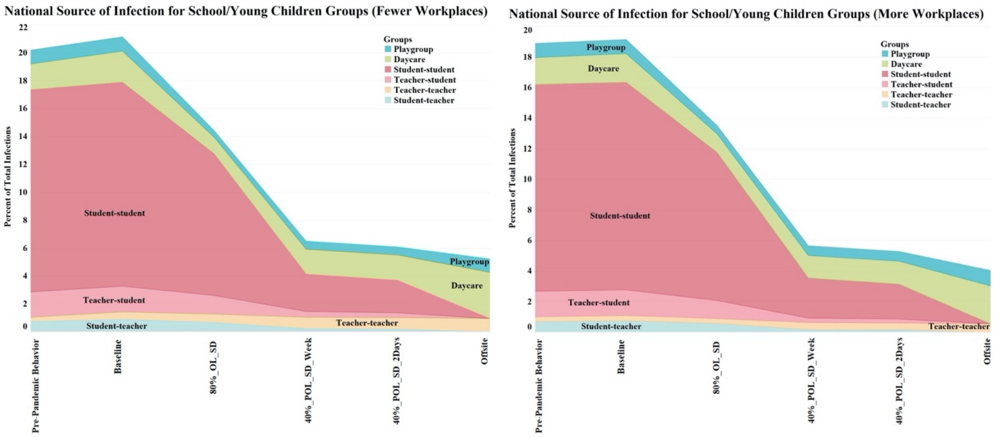

Figure 7. School-related source of infection breakdown including playgroup, daycare, student-student, teacher-student, student-student. The largest contribution is generated from the student-student interactions.

Cases, Deaths, & Hospitalizations Averted

Non-pharmaceutical interventions are effective in averting the potential cases, deaths, and hospitalizations that would have otherwise resulted without the implementations of these public health strategies. We estimated the number of cases, deaths, and hospitalizations that may be averted by comparing each of the mitigation scenarios against the Baseline scenario. Figure 8 shows the cases *averted* and delay to peak incidence for Fewer Open and More Open Workplaces for all the national-level scenarios. The results show that alternating school cohort scenarios can significantly avert the total number of cases by approximately 60M and 28M for the Fewer Open Workplaces and More Open Workplaces, respectively. The results are consistent with previous studies [18, 26-28] that have shown that non-pharmaceutical interventions can delay the peak of an outbreak (i.e., flatten the curve) and reduce the total number of cases over the same time frame. Furthermore, the offsite scenario provides the largest benefit by averting the greatest number of cases followed by the 40% scenarios. Notably, the 100% distance learning scenario averts nearly 5 million more cases and results in almost twice as long time-to-peak interval compared to the split cohort scenarios. These results demonstrate the positive impacts of non-pharmaceutical interventions in reducing disease burden and flattening the curve to allow for healthcare services not to be overwhelmed. Figure 9 shows deaths and hospitalizations *averted* for Fewer Open and More Open Workplaces for all the national-level scenarios. The results show a significant reduction in deaths and hospitalizations for the 40% 2-day/alternating week and offsite scenarios under Fewer Open Workplaces assumptions. Specifically, over 1.6M hospitalizations and 100K deaths may be averted for all 40% and offsite scenarios under the Fewer Open Workplaces assumptions.

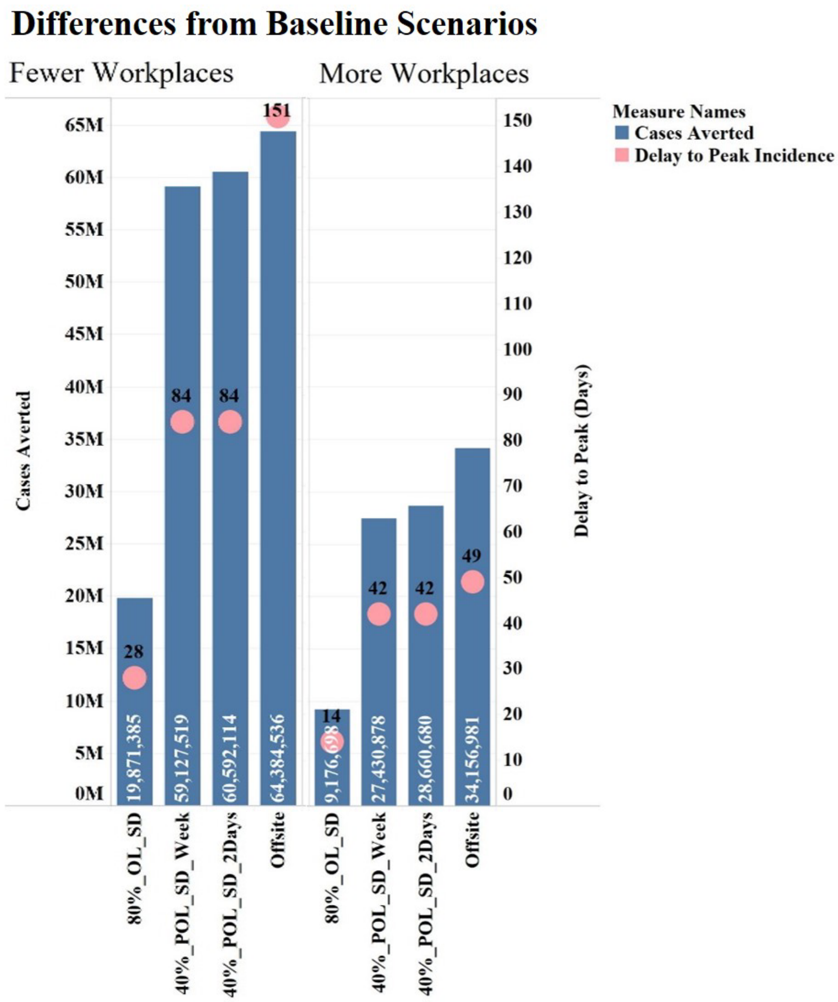

Figure 8. Cases averted and delay to peak incidence in days for all national-level scenarios. Fewer people physically at work and more social distancing along with hybrid school scenarios avert the most cases and delay the peak.

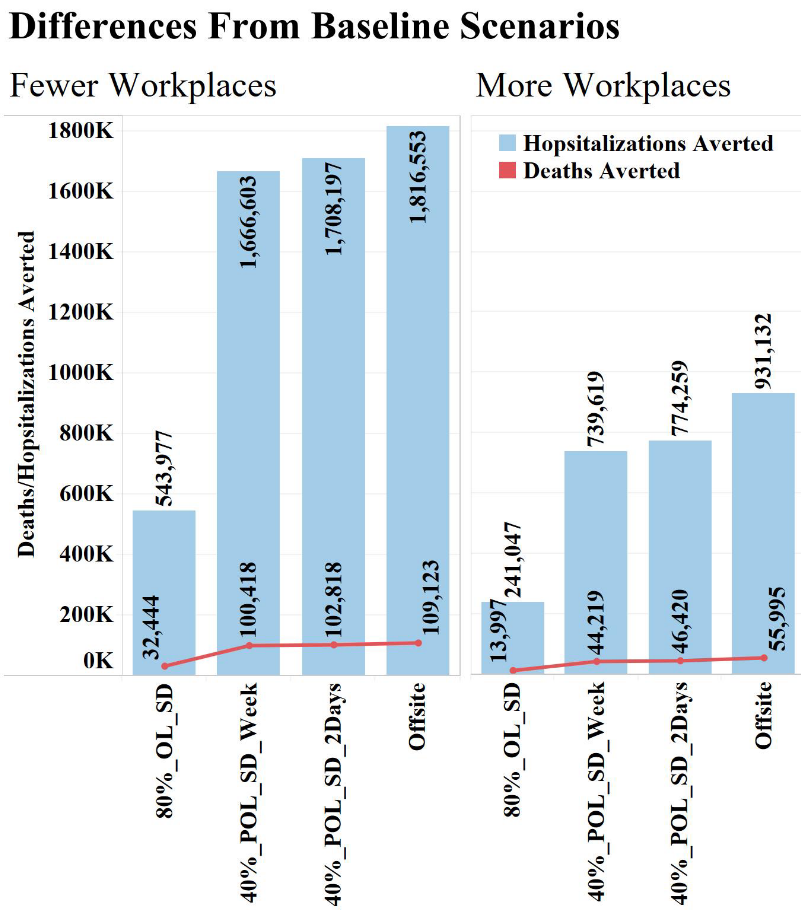

Figure 9. Deaths and hospitalizations averted for all national-level scenarios. There is a significant reduction in deaths and hospitalizations for the 40% 2-day/alternating week and offsite scenarios under Fewer Open Workplaces assumptions

Impacts by Age

We have observed significant variation in the distribution of cases, hospitalization, and deaths by age throughout the pandemic. Notably, during the early stages of the pandemic, older adults were most affected but the age distribution has changed as the pandemic has progressed [29].Given the demographic granularity of EpiCast, we stratified the total cases, hospitalizations, and ICU beds by age group for all national-level scenarios for Fewer Open Workplaces (Figure 10) and More Open Workplaces (see Appendix and Supplemental Files SF1-SF3). Our results show that the highest number of cases for most scenarios is generated by the 5-18 school-aged group followed by the 30-64 age group. However, adults 30-64 years old make up the largest number of hospitalizations and ICU bed usage for all scenarios. It is worth noting that the age distribution of cases for our simulated scenarios looks different than current COVID-19 age distribution for the nation [30]. While the majority of the cases currently reported were during periods when schools were closed and many children were in isolation, we suspect that as schools open and more children are exposed, the case rates for younger populations may increase. Additionally, there may be other factors contributing to these discrepancies including underreporting due to asymptomatic infections, lack of widespread testing [31], initial parameter estimates, and contact patterns assumptions. Specifically, recent evidence suggests that children are more likely to be asymptomatic [32-34] resulting in biased estimates for this population; however, states that have implemented widespread testing, have reported different age distributions [35]. In addition, the initial planning scenarios and subsequent age breakdowns [20] reflected the hospitalization and case fatality age distributions, not the case distribution of infections, which were closer to the relative population of each age group. Finally, our simulated results used contact patterns based on historical estimates for influenza studies due to lack of contact patterns needed to parameterize our model. However, as more evidence becomes available, we will update our assumptions in order to better assess the impacts of COVID-19 by age.

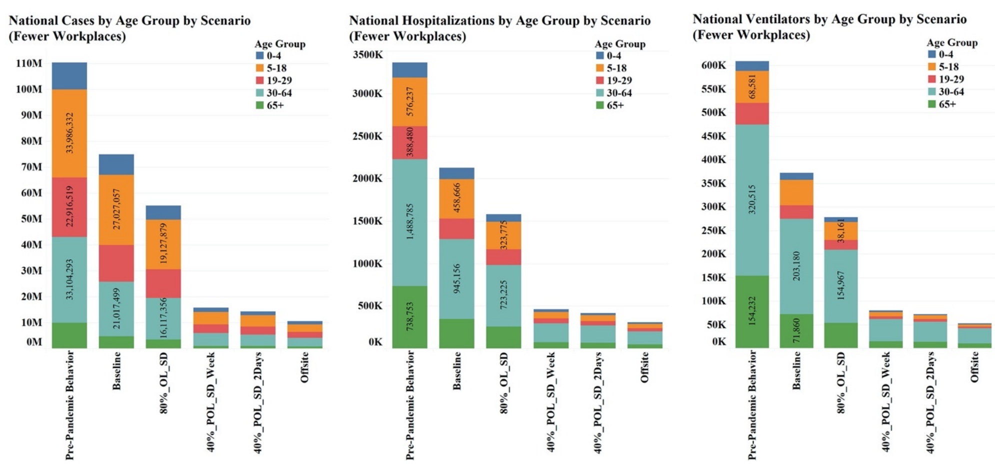

Figure 10. Total cases, hospitalizations, and ICU beds by age group for all the national-level scenarios for Fewer Open Workplaces. Social distancing combined with hybrid school scenarios result in the lowest number of cases.

State-level Comparisons

Spatial heterogeneity has been evident during the COVID-19 pandemic due to local demographics and public health orders implemented across the states. We selected 12 representative states (at least one state per U.S. Department of Health & Human Services Regions) in order to show the spatial differentiation for all the scenarios. Figures 11-12 show normalized epidemic time series and peak day comparisons for 12 states for the baseline and offsite scenarios (additional figures are included in the Appendix). For the baseline with Fewer Open Workplaces, the peak date ranges from October 21st, 2020 (California) to December 10th, 2020 (Maine). The peak is dependent on the current transmission levels for each of these states (i.e., states with higher transmission peak first and states with lower transmission peak later). Note that the offsite scenarios result in flat epidemic curves.

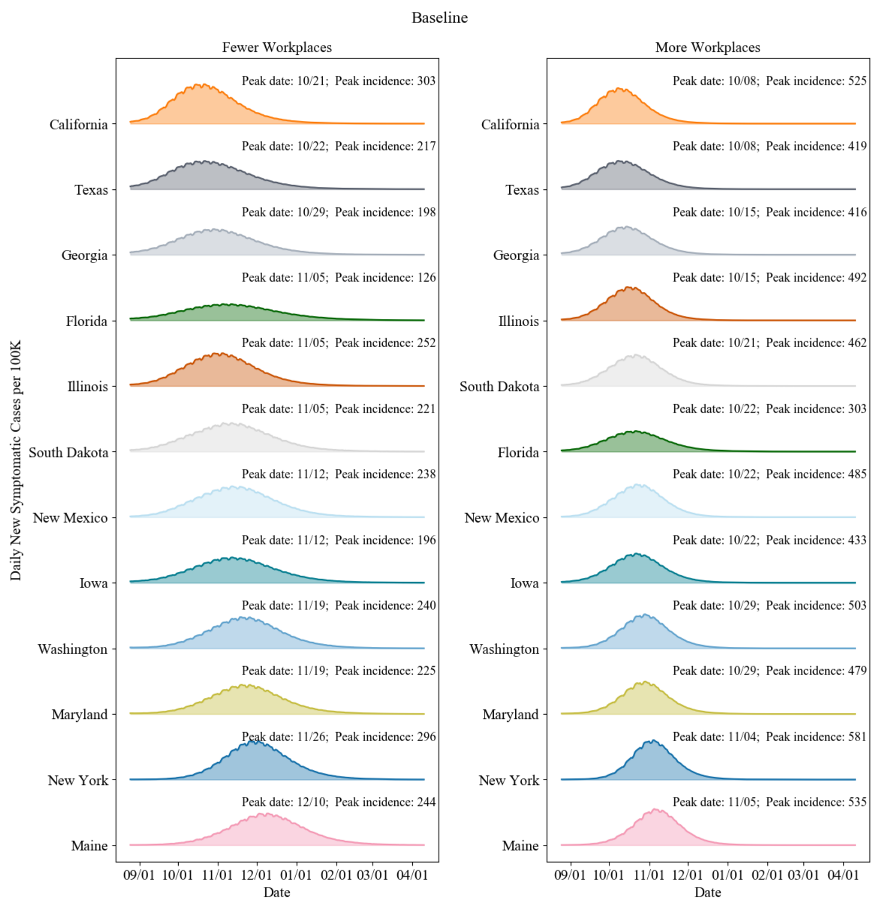

Figure 11. Baseline epidemic curves and peak dates for 12 representative states. (States are sorted by peak date for both scenarios.)

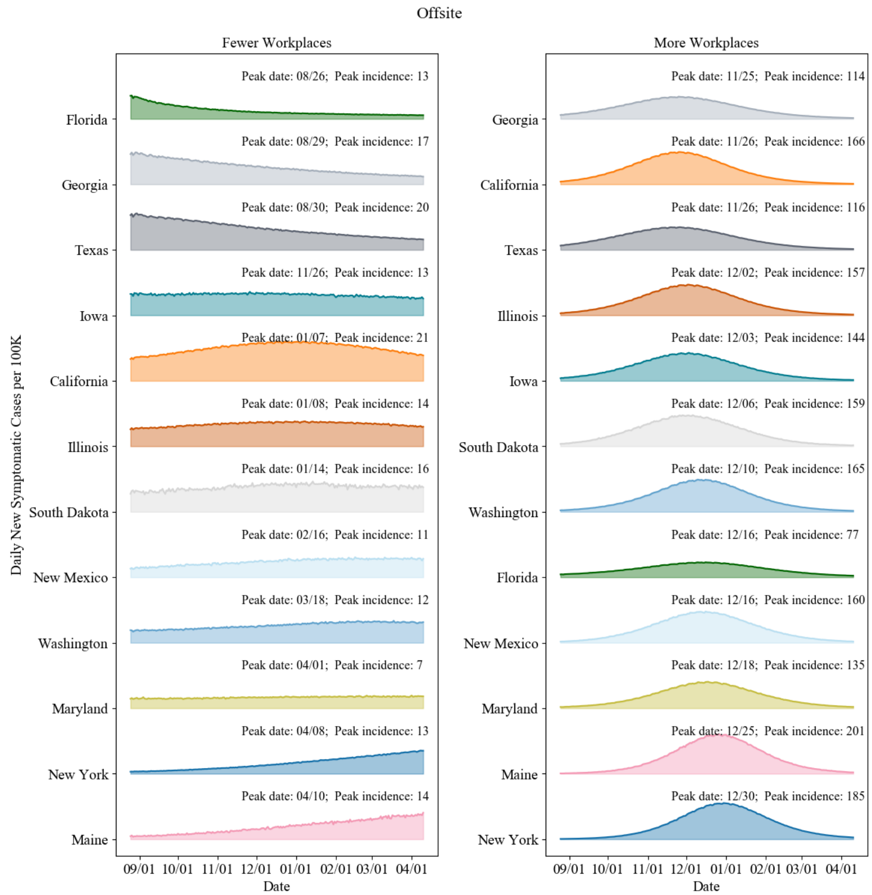

Figure 12. Offsite epidemic curves and peak dates for 12 representative states. (States are sorted by peak date for both scenarios.)

Figure 13 shows epidemic time series and peak day comparisons for 12 states for the 40% 2-day split cohort scenario for both Fewer Open Workplaces and More Open Workplaces. As mentioned earlier, these intervention strategies flatten the curve subsequently delaying the peak. However, the benefits of the cohort scenarios are reduced when more workplaces are open, increasing the transmission paths for the entire population. We note great variability in the impacts and dynamics across the 12 states, especially for the More Open Workplaces scenarios.

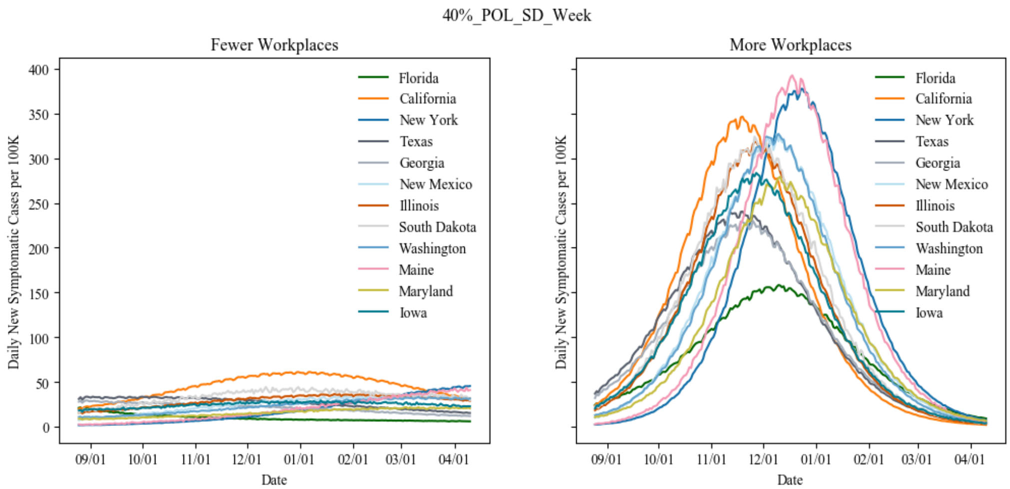

Figure 13. 40% onsite alternating week epidemic curves for 12 representative states

4. Discussion and Conclusions

Non-pharmaceutical interventions such as school closures and social distancing have been implemented globally to mitigate the spread of COVID-19. Given the start of the new school year, there is a need to assess how to best resume school activities while reducing the risk of increased transmission. We used an agent-based simulation to assess the impact of several school reopening scenarios in combination with community level transmission that accounts for workplace in-person restrictions.

Our results suggest that reducing the number of students by 20% (consistent with the percentage of parents who will likely keep children out of school during the school year 2020/21 [25]) reduces the CAR by at least 5% compared to the ~100% enrolment, which would be expected in pre-pandemic period. Scenarios where split cohorts of 40% of students return to school in non-overlapping formats may result in more significant decreases in the CAR, potentially by as much as 75%. The split cohort scenarios have impacts which are modestly lesser than the 100% offsite or distance learning scenario. However, the 100% distance learning scenario averts nearly 5 million more cases and results in almost twice as long time-to-peak interval compared to the split cohort scenario. Alternating school cohort scenarios can also significantly avert the total number of cases by approximately 60M and 28M for the Fewer Open Workplaces and More Open Workplaces, respectively. These split cohort scenarios assume appropriate non-pharmaceutical interventions such as social distancing and wearing facemasks at school. Our results indicate that implementing smaller classroom sizes and cohorts of students with breaks between in-person school attendance (e.g., two days on, three days off) can have a major impact on the spread of COVID-19 both in terms of total cases and timing of the peak of a given outbreak wave.

Increasing the number of in-person workplaces (i.e., from Fewer Open to More Open Workplaces) increases the overall CAR for all scenarios. For the alternating school cohort scenarios, there is a nearly five-fold increase in the CAR when moving from Fewer Open to More Open Workplaces. Implementing both maximum work-from-home and cohorts in school along with social distancing measures will reduce transmission, hospitalizations, and deaths. We observe significant heterogeneity within the U.S. due to the starting initial conditions of current cases, local demographic drivers (i.e., age distribution), and the number and type of workplaces. Areas with high incidence at the beginning of the simulation have worse outcomes and, generally, earlier peaks. This could mean that timing school reopening to coincide with locally lower incidence rates is important. Allowing 100% of students to return back to school is likely to lead to additional increases of infection under the current transmission dynamics in the U.S. and if schools reopen at the 80% or 100% level, school-age children could generate the largest number of cases. All scenarios where schools open even at the 80% levels will result in greater COVID-19 case rates requiring higher levels of hospitalizations, ICU beds, and ventilators needed across the U.S. However, implementing cohorts and smaller class sizes result in fewer cases and deaths, while providing important educational opportunities for children. Combining these with social distancing measures including mask wearing, meeting outside, and keeping distanced from others results in many fewer cases.

Our findings should be considered in context of several potential limitations. First, the model assumed the same level of workplace restrictions (namely Fewer Open Workplaces and More Open Workplaces) uniformly across all the states in the United States in order to compare the different scenarios under similar conditions. However, there is evidence that each state has implemented different public health actions resulting in drastically distinct operating statuses for businesses that have reopened [36]. Therefore, incorporating the heterogeneity in state actions may be necessary in order to better quantify the impact of school reopening scenarios on COVID-19 spread. Second, we did not consider testing and contact tracing explicitly in the simulation. Although we assume isolation of symptomatic individuals promptly after symptom onset, we know that effective contact tracing and testing, in combination with hybrid school reopening scenarios and social distancing measures, will be critical for safely reopening schools. Third, we projected epidemic trajectories through the beginning of April 2021 in order to assess the potential impact of school reopening scenarios during the autumn and winter months. However, several studies [37] have shown that behavioral responses to an epidemic or pandemic are highly dependent on the perception of the severity of the disease. Thus, we expect the behavior and compliance to change and fluctuate in the next six months as a result of new public health orders and disease perception; however, we do not have adequate data to predict this, and therefore assume that the same level of restriction and compliance to non-pharmaceutical interventions will remain in place. Fourth, the population distribution in EpiCast is based upon the 2000 U.S. Census data, to take advantage of the tract-to-tract work flow data that was last compiled then. This is a major limitation for areas that have seen significant population changes in the last two decades, therefore, the simulation may be conservative in terms of the potential contacts and spread of COVID-19. Finally, the epidemiological parameters have spatial and temporal variability during the course of the COVID-19 pandemic. Therefore, additional studies are needed in order to quantify the impact of changing these assumptions on the epidemic projections.

While there is uncertainty in our epidemic projections, our results are consistent with previously published studies [18, 26-28] and are intended to serve as guideposts for deliberations regarding the potential relative impact of different school reopening scenarios in the U.S.

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Appendix –Figures & Tables

Tables A-1 and A-2 show the key results from the modeling for the Chicago MSA region. Table A-1 shows the total number of cases, deaths, and hospitalizations for each scenario for the full simulation period and for the four weeks around the peak of the epidemic. Table A-2 shows the cumulative and peak incidence (and prevalence) as well as the time to peak and the total CAR for each scenario. It is worth noting that both the 2-day and alternating week school scenarios lead to similar CARs in spite of differences in the reduced social distancing assumptions. For Fewer Open Workplaces, ideal social distancing results in a CAR of 5.8% and 6.5%, respectively for the 2-day and alt-week scenarios, rising to 8.8% and 9.7%, respectively with less social distancing. More Open Workplaces results in significantly higher CAR of 29.2% and 29.7%, respectively with ideal social distancing, and 29.7% and 30.3%, respectively with less social distancing. Likewise, peak timing is spread out significantly under Fewer Open Workplaces due to the impact of these partial reopening scenarios in flattening the curve.

Table A-1. Summary of key EpiCast results for Chicago MSA region – Part 1

Workplace Assumptions	Scenario Name	During Peak 4 Weeks			August 15, 2020 to April 11, 2021		
		Cases	Hospitalized	Deaths	Cases	Hospitalized	Deaths
Fewer Open Workplaces	Pre-Pandemic Behavior	2,159,213	60,974	3,163	3,400,697	99,928	6,449
	Baseline	995,674	26,834	1,402	2,466,645	67,484	3,867
	80%_OL_SD	527,005	14,501	787	1,876,690	52,036	2,980
	80%_OL_LessSD	660,681	18,117	965	2,068,149	57,186	3,253
	40%_POL_SD_Week	82,602	2,348	138	515,501	14,401	818
	40%_POL_SD_2Days	70,226	1,990	117	457,062	12,810	733
	40%_POL_LessSD_Week	134,122	3,773	220	763,588	21,187	1,207
	40%_POL_LessSD_2Days	119,614	3,392	185	694,637	19,392	1,084
	Offsite	45,415	1,286	76	339,314	9,571	558
More Open Workplaces	Pre-Pandemic Behavior	2,387,805	69,185	3,669	3,586,058	106,262	6,804
	Baseline	1,811,617	50,808	2,587	3,206,736	92,648	5,679
	80%_OL_SD	1,397,360	40,040	2,200	2,928,719	85,311	5,293
	80%_OL_LessSD	1,450,481	41,658	2,274	2,964,029	86,382	5,316
	40%_POL_SD_Week	712,232	21,100	1,270	2,337,759	69,556	4,361
	40%_POL_SD_2Days	682,950	20,261	1,222	2,297,503	68,493	4,282
	40%_POL_LessSD_Week	747,026	22,083	1,336	2,382,261	70,857	4,469
	40%_POL_LessSD_2Days	717,028	21,208	1,275	2,341,499	69,694	4,374
	Offsite	579,268	17,320	1,055	2,107,852	63,272	3,976

Table A-2. Summary of key EpiCast results for the Chicago MSA region – Part 2

Workplace Assumptions	Scenario Name	Peak Incidence (Cases per 1000)	Time to Peak Incidence (days)	Peak Prevalence (Cases per 1000)	Time to Peak Prevalence (days)	Clinical Attack Rate (%)
Fewer Open Workplaces	**Pre-Pandemic Behavior**	92,048	69	63.4	72	43.2
	Baseline	38,677	97	26.9	101	31.3
	80%_OL_SD	19,844	125	13.9	129	23.8
	80%_OL_LessSD	24,911	118	17.4	122	26.3
	40%_POL_SD_Week	3,011	188	2.1	205	6.5
	40%_POL_SD_2Days	2,559	201	1.8	206	5.8
	40%_POL_LessSD_Week	4,911	188	3.5	192	9.7
	40%_POL_LessSD_2Days	4,383	188	3.1	192	8.8
	Offsite	1,648	174	1.2	178	4.3
More Open Workplaces	**Pre-Pandemic Behavior**	102,256	65	71.4	70	45.6
	Baseline	74,889	76	51.8	80	40.7
	80%_OL_SD	54,907	83	38.5	87	37.2
	80%_OL_LessSD	57,771	83	40.3	87	37.6
	40%_POL_SD_Week	26,489	110	18.7	115	29.7
	40%_POL_SD_2Days	25,471	117	17.9	119	29.2
	40%_POL_LessSD_Week	27,952	110	19.7	115	30.3
	40%_POL_LessSD_2Days	26,823	110	18.9	115	29.7
	Offsite	21,484	118	15.2	122	26.8

Figures B-1 to B-7 show epidemic time series for 12 states for all the scenarios not shown in the main manuscript for both Fewer Open and More Open Workplaces. Data for all other states (including the ones shown here) are provided as supplemental material under Supplemental Files SF1-SF3.

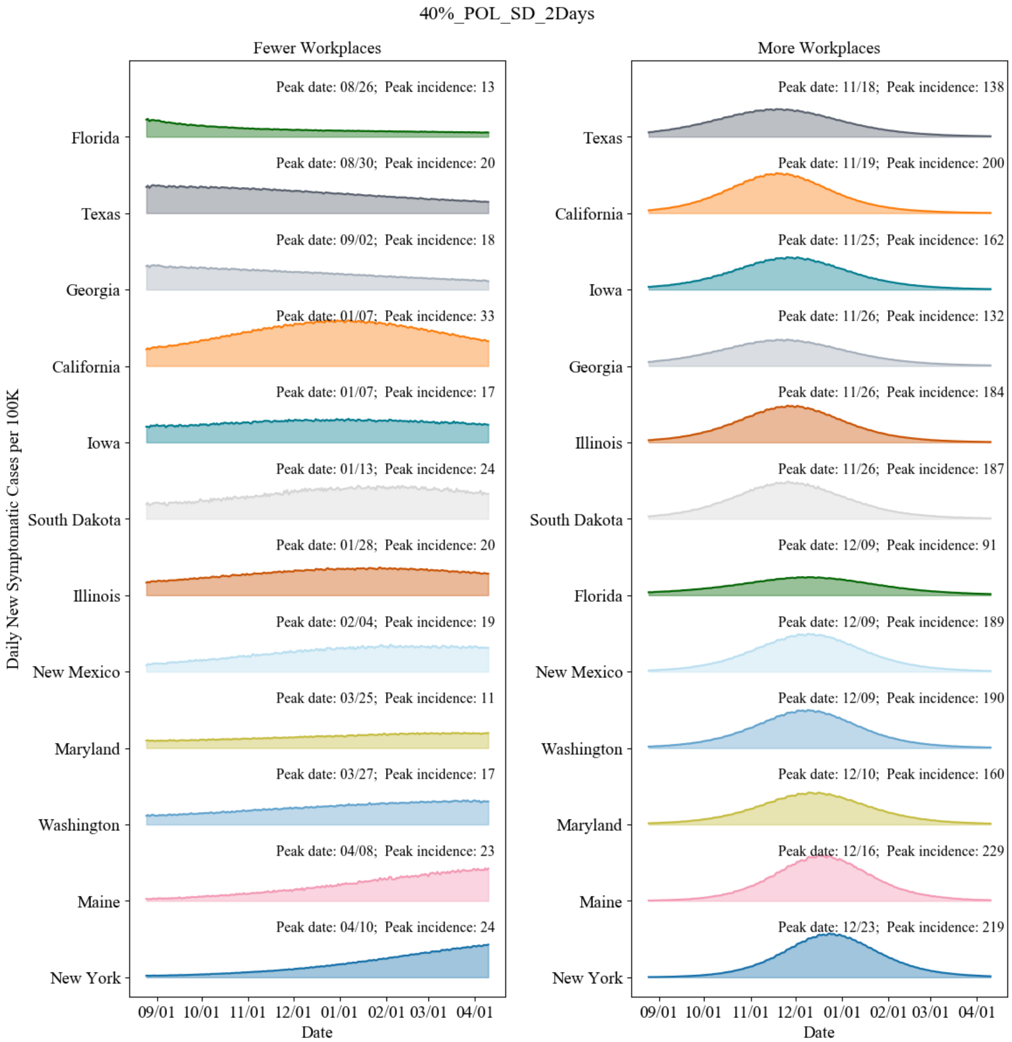

Figure B-1. 40% onsite 2-day epidemic curves and peak dates for 12 representative states. (States are sorted by peak date for both scenarios.)

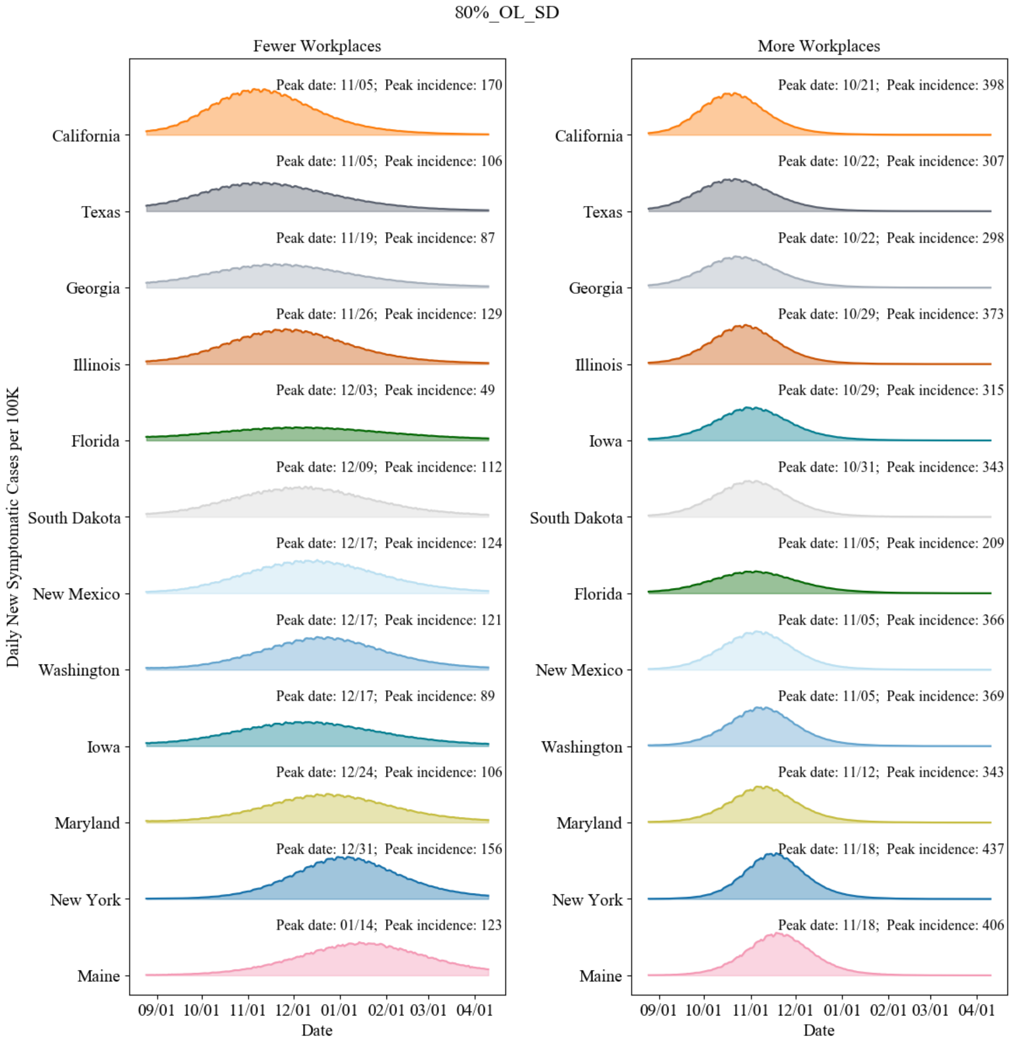

Figure B-2. 80% onsite epidemic curves and peak dates for 12 representative states. (States are sorted by peak date for both scenarios.)

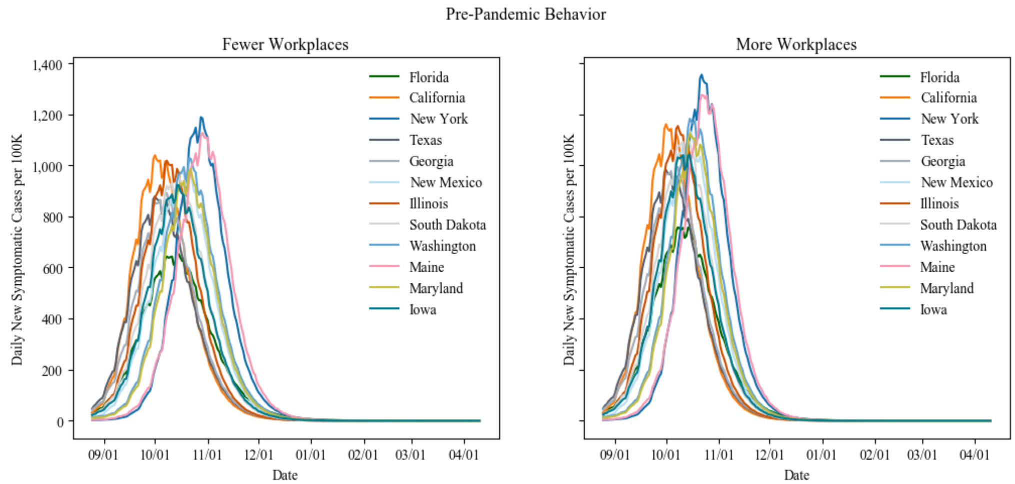

Figure B-3. Pre-pandemic Behavior epidemic curves for 12 representative states

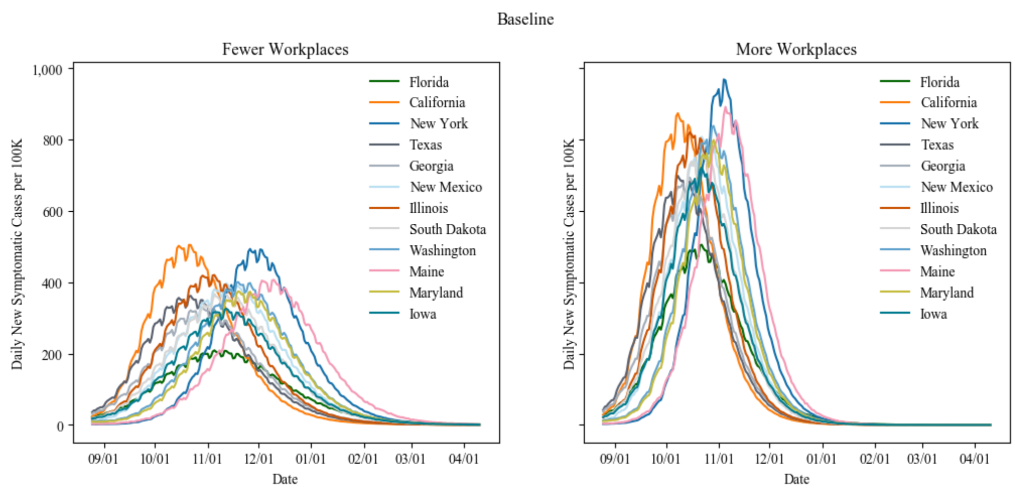

Figure B-4. Baseline epidemic curves for 12 representative states

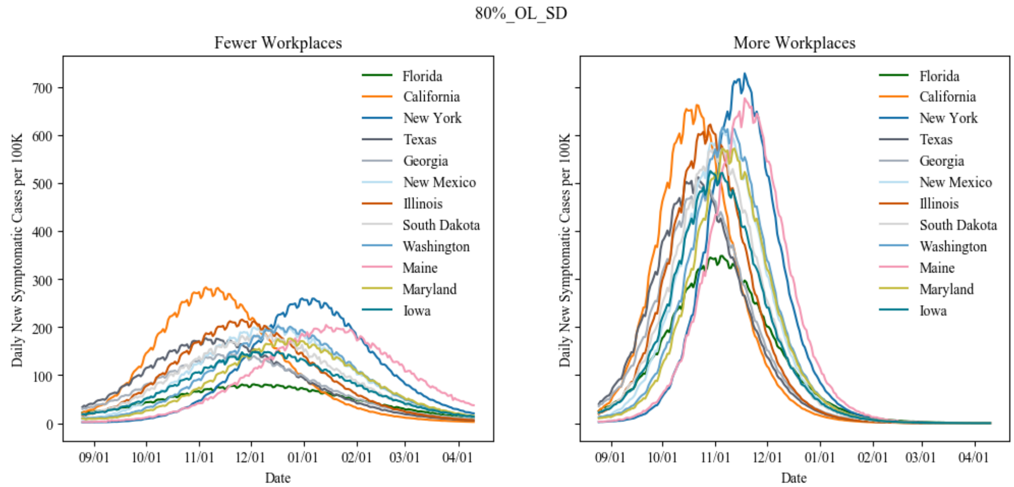

Figure B-5. 80% onsite epidemic curves for 12 representative states

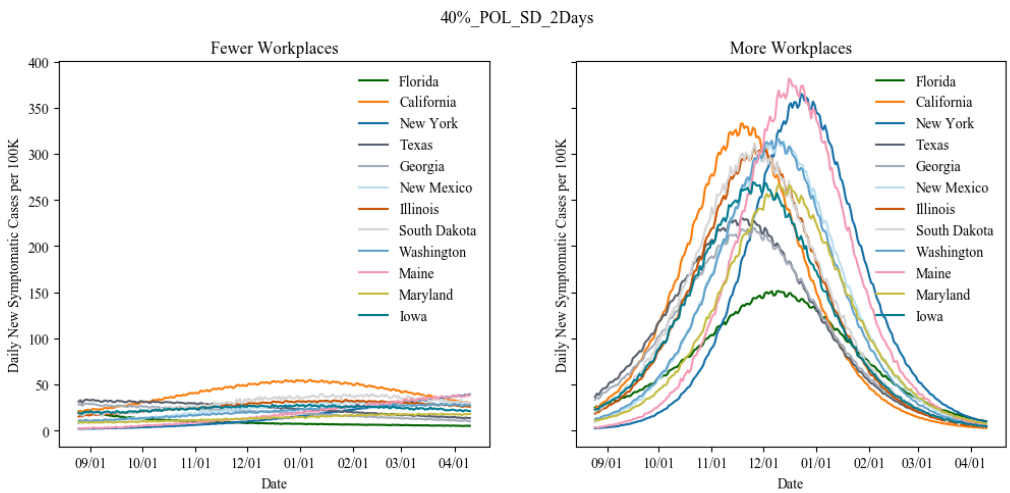

Figure B-6. 40% onsite 2-day epidemic curves for 12 representative states

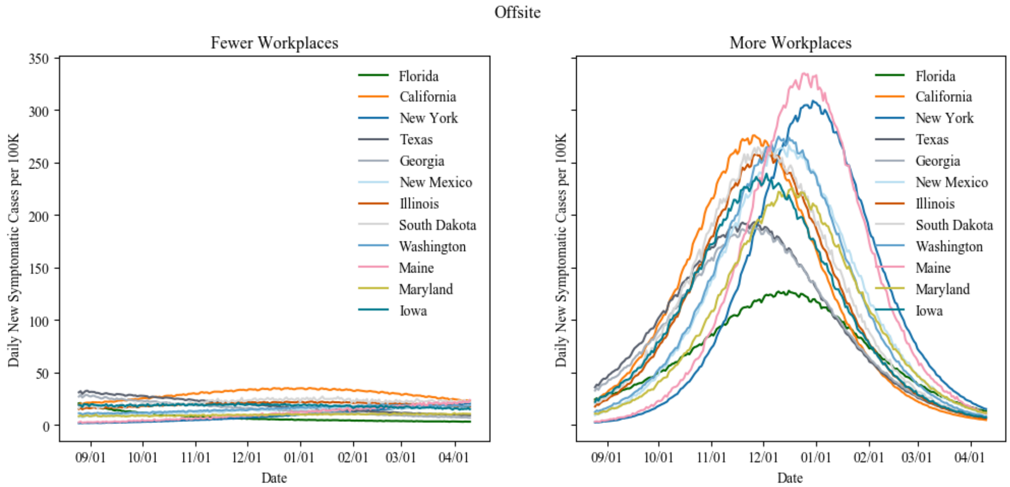

Figure B-7. Offsite epidemic curves for 12 representative states

Figure B-8 shows the source of infection as a percentage aggregated at the national-level for all the scenarios for both Fewer Open and More Open Workplaces.

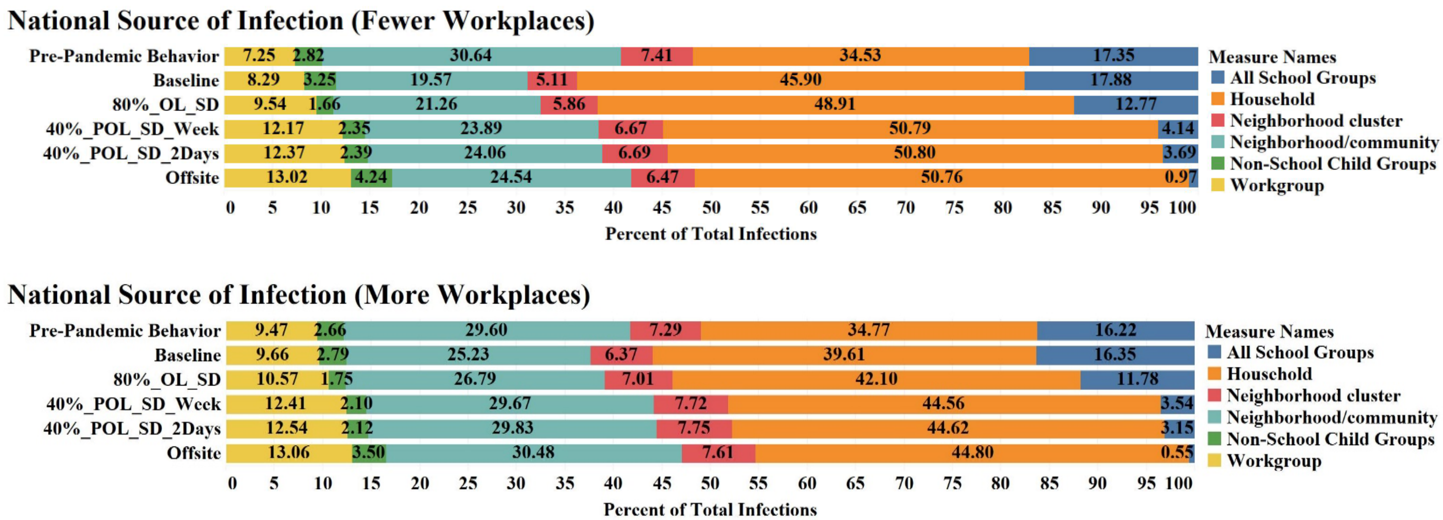

Figure B-8. Source of infection for scenarios aggregated for all states.

Figure B-9 shows the total number of cases, hospitalizations, and ICU beds by age group for all the national-level scenarios for More Open Workplaces.

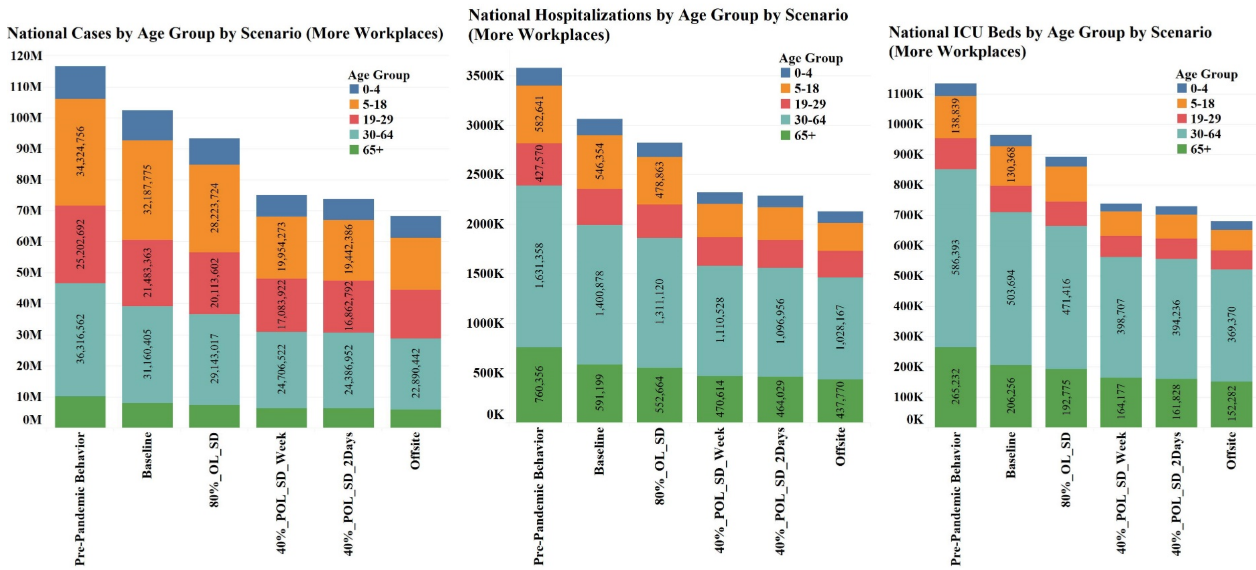

Figure B-9. Total cases, hospitalizations, and ICU beds by age group for all the national-level scenarios for More Open Workplaces.

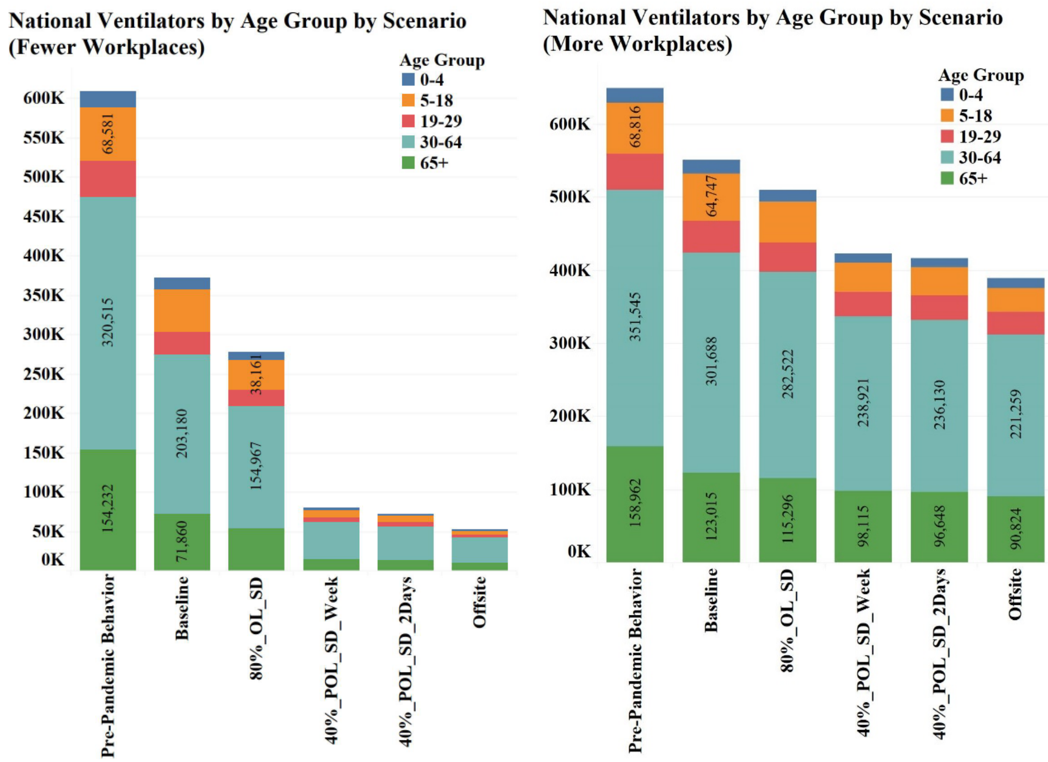

Figure B-10. Total ventilators used by age group for all national-level scenarios.

What Happens Next

FEBRUARY 01, 2021

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Craig Tyler | Editor

Inside the Herculean effort to anticipate the path of the virus and mitigate its impact

“The outbreak should follow the same process in every community,” says Los Alamos scientist Ben McMahon. “At least in theory. It should get worse and worse until the community realizes they have to get serious about isolating, and then it should fall away quickly. The epidemic curve is really a learning curve.”

But the COVID-19 outbreak is far from a textbook event, and McMahon, a key player in Los Alamos’s comprehensive effort to model the pandemic, is knee-deep in all the ways the learning curve can be distorted. In a joint enterprise to model the pandemic for better-informed policymaking, Los Alamos shares detailed weekly reports with three other national laboratories, and every single week—even after the better part of a year—surprising, fundamental new information is still coming to light. For a disease that stubbornly carves out an exception to nearly every rule the experts try to attach to it—from the symptoms it produces to the effectiveness of the antibodies its survivors retain—McMahon and his colleagues strive to assemble the most believable set of “facts” possible and feed them to a computer to answer one question: What is likely to happen next?

“The trouble is”—McMahon has to interrupt himself here—“well, one of the many troubles is: Susceptibility varies greatly depending on age, sex, and certain preexisting conditions. That means some people are substantially less likely to die, get tested, or even show any symptoms, even though they may be every bit as likely to transmit the virus.” With something like Ebola, everyone is suitably terrified, young and old, and the learning curve is very steep: isolate or die. With COVID-19, the weight of the message is considerably more fragmented.

Uncertainties about both the contagion itself and the personal and societal behaviors that contribute to either its spread or its containment greatly complicate researchers' efforts to predict the course of the pandemic. But that information is absolutely crucial. If policymakers know the potential landscape of tomorrow, they will have a much better idea of what to do about it today.

What will happen

Los Alamos has a number of COVID-modeling efforts underway. The most widely shared of these is on its public website and featured on the Centers for Disease Control (CDC) website as well, due to its track record for accuracy. The model spans the globe, country by country, and the United States, state by state. It is produced and managed by a team of about 20 Los Alamos specialists, including computer scientists, bioscientists, mathematicians, economists, and others; statistician Dave Osthus leads the team.

"Our model produces forecasts, not projections," Osthus explains. "Whereas a projection predicts what *would* happen if various strategies were put in place or various circumstances came to pass, a forecast directly predicts what *will* happen based on what is already happening." That doesn't mean it ignores policy interventions, such as stay-at-home orders—far from it. But rather than trying to figure out how much of a difference they *ought* to make, the model examines how much of a difference they are already making or how much difference they have already made elsewhere. The result is an ultimate best-guess at the future—cumulative confirmed cases and deaths—driven by real-world data.

Unlike flu, there is no historical data on COVID-19—no benefit of hindsight.

Real-world data, however, are not especially straightforward. Actual cases are sharply different from confirmed cases; confirmed cases result from testing, and testing is not uniformly accurate. And even if all COVID-19 tests were perfectly accurate, there would still be a huge question mark when it comes to who is getting tested. How many people? Which ones? People who are already sick? People who visit a clinic for some other reason? Or a cross section of the public at large? There is tremendous variation in procedures from state to state and even county to county, since much of this data is obtained by public health departments at the county level. The Los Alamos statistical model has to deal with these challenges and generate the most reliable prediction possible anyway.

To do that, the model has to learn; it has to assimilate large amounts of data and figure out how to recognize trends, broken down by region. It also has to learn from its mistakes. As events unfold and new data are gathered from one week to the next, the model must attempt to improve itself.

Fortunately, Osthus had already been working with just such a machine-learning model, called Dante, to predict recent flu seasons. In a contest sponsored by the CDC for the 2018–2019 flu season, 24 teams submitted model output, and Dante's predictions came closest to matching reality. Osthus and others reworked it for the COVID-19 pandemic.

However, COVID-19 and flu have two important differences, in terms of modeling. The first is the fact that people have been dealing with the flu for ages, and there is a lot of valuable historical data to work with, but not for COVID-19—there's no benefit of hindsight. All the data on COVID-19 comes from the current pandemic in real time. To put it bluntly, the forecast gets more accurate if more people get sick and die.

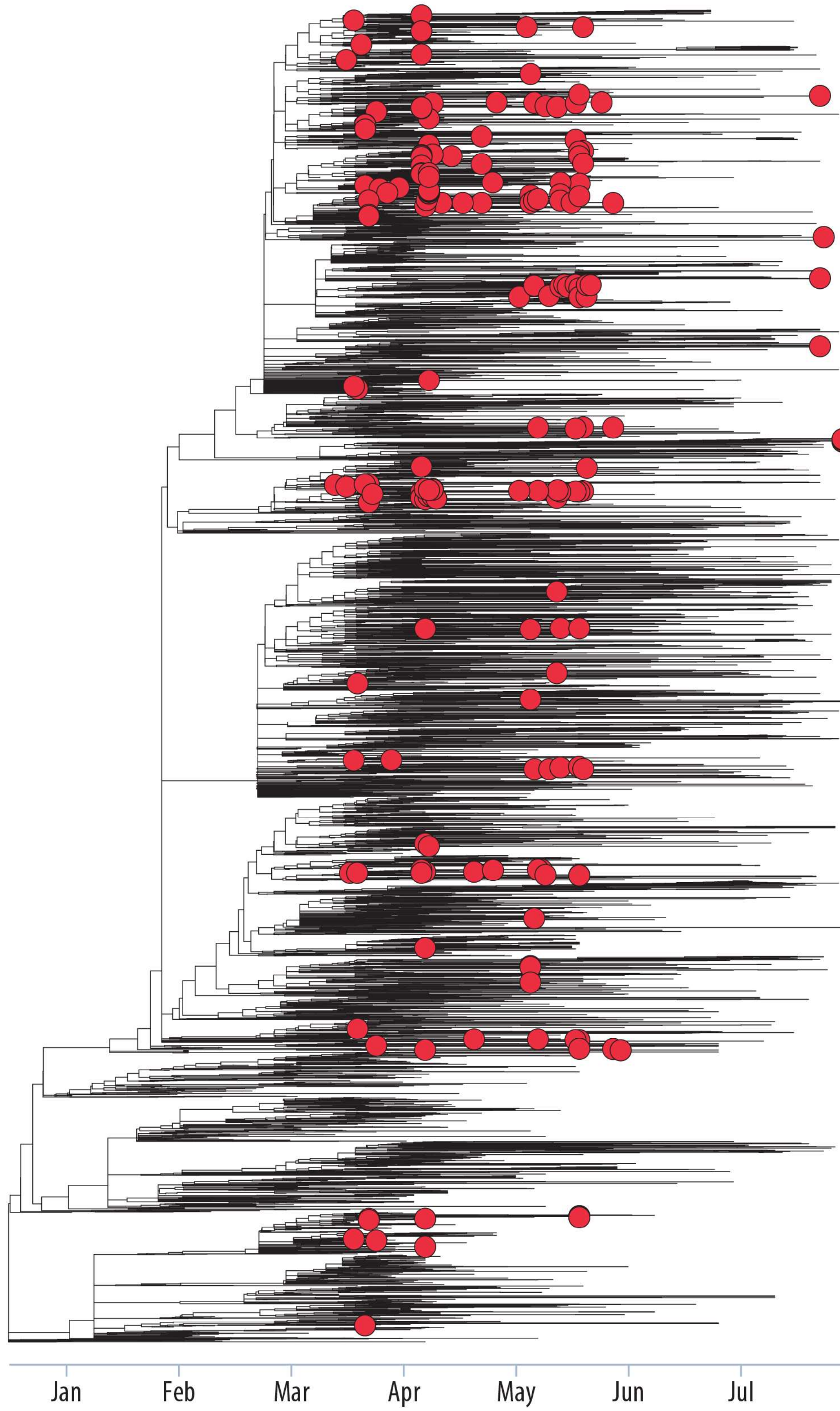
The other major difference between the current pandemic and the flu stems from individual behavior. Because flu is so familiar, the range of human behavior is not very wide. A relatively consistent fraction of infected people will go to work anyway, despite feeling sick. A relatively consistent fraction of people will see a doctor. A relatively consistent fraction of people will get a flu vaccine each year. It is through this similarity from season to season that a gigantic source of uncertainty—human behavior—can be tamed. But with COVID-19, individual behaviors are critical, and there is no historical basis to justify anything modelers might assume. Hand washing, face masks, social distancing, restricted travel—such things vary to a large degree and are extraordinarily difficult to predict or even assess after the fact. How often did residents of Hawaii or Ohio wash their hands in the past month? How seriously did they adhere to social distancing mandates?

Without knowing the answers to these kinds of questions, it's difficult to predict the future. It's even more difficult to determine which interventions would be the most effective. But just because individual behavior is difficult to quantify doesn't mean Los Alamos scientists can't find a way to model it.

What would happen

A trio of cause-and-effect, rather than statistical, Los Alamos models is intended to address what-if questions. What would happen if schools ramp up onsite learning? Or if non-pharmaceutical interventions, such as face masks, social distancing, and hygiene measures, were intensified (or reduced)? Or if a vaccine were distributed in a particular way?

Perhaps the most straightforward of these models is EpiGrid, an epidemiological model that tracks the geographic spread of a disease by breaking the landscape into a connected grid of 10-kilometer-square regions, rather than administrative units like countries, states, or counties. Originally developed as a risk-assessment tool for bioterror attacks and natural pandemics, EpiGrid is comprehensive and versatile, making do with imperfect data. Scenarios have been developed for many countries, pathogens, and assumed responses.



2020

Phylogenetic modeling of SARS-CoV-2 genome sequences reveals the relatedness of groups of infections over time. Each horizontal line represents a viral lineage and terminates at the time when that genome was sampled. Lines that end in red circles are from New Mexico cases; tight groupings of red circles, therefore, suggest clusters of New Mexico infections with a common source, possibly a single introduction into the state followed by transmission within it. However, the large number of New Mexico cases widely separated on this figure suggest a great many introductions arriving at different times (from the Mountain West as well as elsewhere in the country and the world).

EpiGrid accounts for details of the infectious agent itself (How long does it incubate? How is it transmitted—droplets, contaminated water, mosquitoes, etc.? Are asymptomatic or pre-symptomatic people contagious? Can people who have recovered be infected again?), the progression of the disease

(How many people are susceptible? Exposed? Infected? Seriously ill or hospitalized? How many have recovered? How many have died?), the modes of treatment (Antivirals? Vaccines? Other treatments?), and societal actions (Are quarantines in place? Are masks required? Are schools open?).

"Los Alamos has been doing epidemiological modeling for decades, starting with HIV," says Paul Fenimore, EpiGrid project leader. "It's a capability we were very wise to develop." For the sudden emergence of COVID-19, Fenimore and his colleagues strive to make EpiGrid as reliable as it already is for infections like plague or cholera. So they work the problem in both directions: in January, they forecast February, and in February, they retroactively assess what did and didn't work in the forecast in January.

Another key model, EpiCast, has similarly deep roots—but from a completely different kind of soil. Rather than being built from the ground up for epidemiology, EpiCast was adapted from an earlier materials-science model designed to support nuclear weapons technology. Just as individual atoms contribute to the nature of a material, individual infected people contribute to the progression of an epidemic, and the model is structured to treat each element (atoms or people) in an agent-based fashion, tracking its influence and that of its neighbors to their ultimate global effects. Whereas EpiGrid typically covers large regions in aggregate (e.g., the eastern half of the country) with medium-grain resolution, EpiCast resolves down to the census-tract level, consisting of only about 2000 individuals, capturing their contact networks and daily travels, as well as any pandemic-related policy restrictions on either.

Not surprisingly, operating a model with such resolution requires a powerful computer. While EpiGrid can run on a laptop, EpiCast requires a supercomputer—and Los Alamos has several. In fact, Los Alamos has long been a key player nationally in high-performance computing (HPC) across the board, always keeping up with cutting-edge hardware, expert personnel, and scientists studying both the complex systems that require HPC for their simulations (e.g., climate models) and the science of HPC itself (such as minimizing error rates and applying different algorithmic approaches). Los Alamos HPC capabilities are currently being shared across a broad consortium of national laboratories and government agencies, universities, and technology companies to make supercomputers—which are normally prohibitively expensive for smaller organizations—freely available to researchers working to combat the virus with computationally intensive tasks such as drug discovery.

With Los Alamos's own agent-based HPC pandemic model, the results are especially credible, since the "agents" are essentially actual Americans: EpiCast incorporates real census counts combined with accurate demographics, school and workforce participation, and public-transit commuter information, among other key parameters. In addition, a key differentiator between EpiCast and other similar efforts is its ability to categorize workers within different industry sectors. This feature proved critical in understanding and projecting the pandemic in the United States by taking into account the variability in work-from-home policies affecting different segments of the workforce. The effects of changing mitigation strategies or individual behaviors thus percolate through an uncommonly realistic representation of the American populace. It is here that Los Alamos scientists Tim Germann, Carrie Manore, and Sara Del Valle can model those difficult-to-model human behaviors and analyze which ones are most effective in slowing the pandemic. As a result, EpiCast has been able to meaningfully assess the impact of reopening schools and workplaces.

What does happen

Inferring the movement of the virus from epidemiological data, such as interviews with infected people to pinpoint where they have been and with whom they have had contact, results in an incomplete picture, making it difficult to calibrate models with real-world data. Los Alamos scientists Emma Goldberg, Ethan Romero-Severson, and Thomas Leitner are therefore tracking the movement of the virus with direct analyses of its genome as it migrates through the human population. Small, natural mutations are always happening to individual viral particles, and they happen at a fairly steady rate of approximately one or two nucleotides (basic elements of genetic code) every one or two weeks. That stream of inherited changes makes it possible to draw conclusions along the lines of whether *this* person could have acquired SARS-CoV-2 from *that* source (person, hospital, city, etc.) over *such and such* a timeframe when the viral genomes are so different.

The epidemic curve is really a learning curve.

By tracing what the mutations show about the relatedness of infections, i.e., the phylogenetics—a capability Los Alamos previously advanced to address the evolution of HIV infections—the scientists can help identify how and when the virus traveled from one region to another. This makes it possible to reliably tease apart whether a resurgence of cases in one area was caused by community spread within that area or by reinfection from the outside. The answer matters: if it's the former, then it might make sense to double down on isolation measures, such as closures and social distancing; if it's the latter, it might be more consequential to restrict interstate travel. In this way, real-world genomic data can be used to identify what happened in specific regions at specific times—and also validate (or contradict) models such as EpiCast, allowing them to more accurately extrapolate and predict the direction of the pandemic across the country.

"Of course, we need up-to-date genome data to make up-to-date inferences," says Goldberg. "That's why we're coordinating with the University of New Mexico, TriCore Reference Laboratories, and the New Mexico Department of Health to continue to get viral genomes as more infections are confirmed in state." She and Romero-Severson are performing sophisticated statistical analyses to pull patterns from this in-state data, combined with other publicly available genomic data shared from across the globe. Such patterns reveal actionable characteristics of the movement of the virus—for example, which groups of cases trace back to a single introduction into New Mexico and how the number of such introductions is changing over time.

Meanwhile, Leitner is comparing current SARS-CoV-2 phylogenetics with those of other recent coronavirus outbreaks, including SARS-CoV and MERS-CoV, and with other types of resident coronavirus infections in animals, such as bats. In addition, a user-friendly web interface for genomic science, built by Los Alamos bioinformatics specialist Patrick Chain and his colleagues, is now being used to help automate the reconstruction of SARS-CoV-2 genomes for inclusion in phylogenetic trees and public genome repositories. The system analyzes the population of viral genomes found in a sample from a COVID-19 patient and identifies specific mutations and their prevalence. There is also a feature for evaluating how effective current high-quality viral-RNA-based COVID-19 diagnostic tests are at recognizing emerging genetic variants. And all of this work—phylogenetic analysis, pattern extraction, comparative studies, genome reconstruction, and diagnostic-test validation—capitalizes on Los Alamos computing technology and expertise.

In addition to geographic, phylogenetic, and behavioral aspects, a final key element of the Los Alamos modeling effort is systemic and capitalizes on a major research initiative from the previous decade. From 2003 to 2010, Los Alamos scientists modeled the nation's critical infrastructure—things like power, transportation, and, of particular relevance now, public health—to expose their interdependencies and learn how to maintain them in a crisis. When the COVID-19 pandemic struck, Los Alamos scientist Jeanne Fair and fellow researchers Rene LeClaire, and Lori Dauelsberg—all of whom were key players in the critical-infrastructure study—responded quickly to restore that capability and adapt it to the current pandemic.

Models have to accept flawed data and generate the best possible prediction anyway.

As part of this process, they had to rework an earlier epidemiological model of an influenza pandemic scenario so that it would properly account for the very different scenario brought on by a coronavirus. The result, known as MEDIAN (Modeling Epidemics for Decision support with Infrastructure ANalysis), is a suite of system-dynamics models designed to identify the key drivers of the pandemic. It explores the large uncertainties pertaining to the disease itself—things like incubation period and mortality rates—together with the way society's infrastructure systems function to make things better or worse.

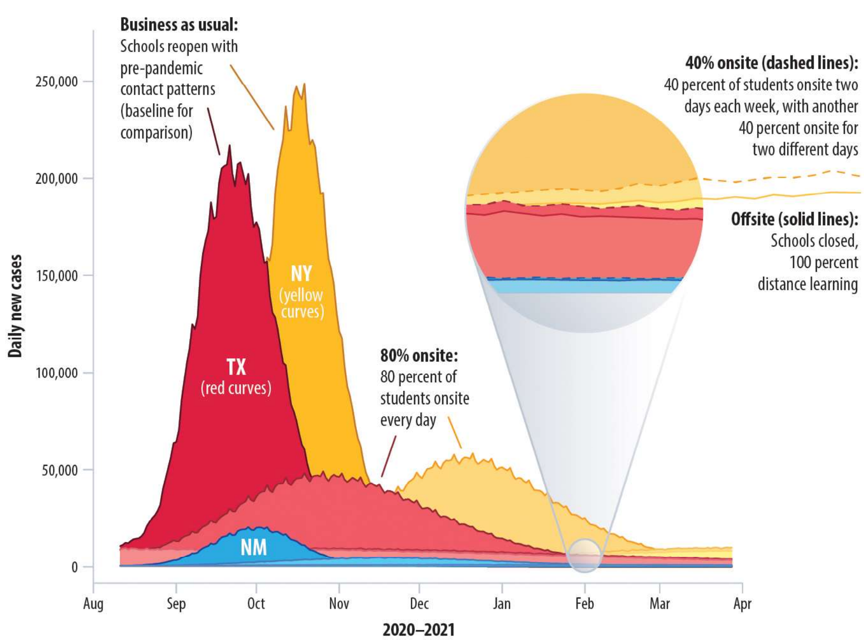
For example, one often hears about the danger of simply “overwhelming the healthcare system,” but the healthcare system is a complicated animal. People are routed among home care, physicians’ offices, hospitals, intensive-care units, emergency rooms, and long-term care facilities. Medical services can include multiple types of COVID-19 testing and treatment, and the selection of services could have significant impacts on the trajectory of the pandemic. The MEDIAN team is looking at which knobs to turn to most affect the outcome, and it has been tasked in particular with understanding the uncertainties associated with testing and diagnostics to help identify an optimal testing strategy.

What should happen

COVID-19 is a killer, and Los Alamos is doing everything it can to provide life-saving scientific guidance for policymakers. The four-lab collaboration between Los Alamos, Argonne, Sandia, and Oak Ridge national laboratories has been fruitful in this regard. Just as Los Alamos is particularly well positioned to provide expansive modeling and diagnostics, partner labs have their own specialties that collectively contribute to overall situational awareness. Ben McMahon, who continues to learn everything he can to help accelerate the nation’s learning curve, is paying close attention.

“Weekly reports between partner labs reveal an ever-expanding, ever-sharpening picture,” says McMahon, “but they also deliver a healthy dose of humility. They increase what we know and refocus our attention on everything we don’t.”

Within Los Alamos’s home state, this knowledge—incomplete though it may be—is making a big difference. Throughout the crisis, Laboratory experts have been in regular contact with New Mexico state officials, hospital representatives, mental health specialists, regional economists, and other policy professionals. Typically, two or three conference calls per week allow vital information to be shared as soon as it is discovered. Additionally, state officials can get scientific evaluations from Los Alamos on the questions that arise day to day, such as whether a new cluster of cases is likely to represent a “real” problem or a statistical blip, or how best to distribute the available COVID-19 tests. Major policy announcements or changes are made only after extensive discussions with a diverse set of experts, including Los Alamos scientists from many disciplines.



Can schools be re-opened safely? Shown here are the projections of an EpiCast model from August 2020, presenting the anticipated number of new cases daily (vertical axis) versus time, assuming different approaches to school re-openings. Compared to a business-as-usual school reopening (tall peaks), reduced onsite learning significantly diminishes peak new cases—flattening the curve to reduce the peak burden on the healthcare system. Reducing to a plan with 40 percent of students onsite at one time (two cohorts, with two days per week for each) cuts new cases down to a rate much closer to that obtained by 100 percent remote learning. The model takes into account the initial conditions in each state (at the time the model was run) and the regional demographics, including how many people work in industries that are still operating onsite during the pandemic. This accounts for the state-by-state differences. As a result, Texas, for example, would see an earlier peak than most other states and New York a later one. New Mexico, home to Los Alamos, would peak in between.

“Los Alamos serves the entire nation with its resources, capabilities, and expertise, but the partnership between Los Alamos and the state of New Mexico has been extraordinarily productive for everyone involved as well,” says Kirsten McCabe of the Lab’s National Security and Defense Program Office. “We are fortunate to be able to interact with the state government and Presbyterian Healthcare Services and to have a proactive governor making informed decisions to manage the crisis. Critical information flows freely in both directions.”

Exponential change goes in both directions, too. If one infected person infects five more, then 25, then 125, the cases will skyrocket. But if one infected person infects one-tenth as many—0.5 on average, say—then exponential growth reverses and becomes exponential decay: 20 cases become ten, ten become five, and any new flare-up dwindles away. If model-informed policies can put the population firmly in the exponential-decay domain, then careful, controlled attempts to restore particular elements of normal life can be attempted relatively safely. With great vigilance to rapidly isolate and contact trace new cases as they appear, the prevailing condition of exponential decay can be relied upon to do its thing.

“The math works with us or against us,” says McMahon, “but it’s a very fine line. It all hinges on having extremely accurate models and acting on the best possible information.”

Like many of his pandemic-modeling colleagues at Los Alamos and around the world, McMahon feels frazzled. But there is no rest. Until scientists know much more about this virus, the weight of the world will continue to hang on a select few, including healthcare workers, elected leaders, and yes, modelers, who continuously reshape shifting uncertainties into the most likely truths. They are, after all, the ones specifically entrusted with advancing our learning curve. **LDRD**

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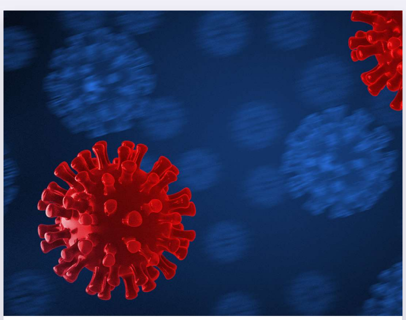

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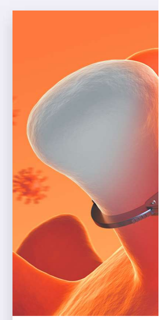

Catching th

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December 17, 2020

Los Alamos National Laboratory (LANL), which operates under the purview of the National Nuclear Security Administration (NNSA), is home to a variety of supercomputers that are typically used for nuclear weapon simulations and related tasks. This year, however, LANL has been spending much of its supercomputing time fighting a different national security threat: COVID-19.

Over the course of the year, LANL has pitted its supercomputing prowess against every aspect of the pandemic, from modeling the virus and its spread to investigating various pharmaceuticals that might mitigate or prevent infections. Now, LANL finds itself facing what may be one of the final challenges posed by SARS-CoV-2: optimizing distribution of the new vaccines that may signal the beginning of the end of COVID-19.

Los Alamos NATIONAL LABORATORY EST.1943

The new vaccines from Pfizer and Moderna have been deemed highly effective by the FDA; unfortunately, doses are likely to be limited for some time. As a result, many state governments are struggling to weigh difficult choices – should the most exposed, like frontline workers, be vaccinated first? Or perhaps the most vulnerable, like the elderly and immunocompromised? And after them, who's next?

LANL was no stranger to this kind of analysis: earlier in the year, the lab had used supercomputer-powered tools like EpiCast to simulate virtual cities populated by individuals with demographic characteristics to model how COVID-19 would spread under different conditions.

“The first thing we looked at was whether it made a difference to prioritize certain populations – such as healthcare workers – or to just distribute the vaccine randomly,” said Sara Del Valle, the LANL computational epidemiologist who is leading the lab’s COVID-19 modeling efforts. “We learned that prioritizing healthcare workers first was more effective in reducing the number of COVID cases and deaths.”

The lab’s modeling results are not merely an academic or aspirational exercise. Throughout the year, state and federal policymakers paid close attention to LANL’s HPC-enabled epidemiological modeling, and the results were directly used to guide policy decisions. The vaccine modeling is no different – in fact, the lab says that the scenarios are being developed in close coordination with local, state and federal officials. This is particularly true of New Mexico, LANL’s home state.

“Our ongoing collaboration with the modeling team at Los Alamos National Laboratory continues as we plan and refine the best ways to distribute the vaccine in a safe, equitable and effective way,” Matt Nerzig, a spokesman for the New Mexico governor’s office, told the *Santa Fe Reporter*. “From the start of the pandemic, we have made every effort to rely on the best possible data and analysis to fight the virus.”

While the vaccines are extraordinarily promising, the researchers caution that the models show they are not yet a silver bullet for the pandemic – and may not be for some time.

“These models very clearly illustrate that, for many months, the vaccine alone isn’t going to be enough to keep us safe,” said Ben McMahon, a mathematical epidemiologist at LANL. “Given the limited vaccine supply and the fact that immunity builds steadily for several weeks after vaccination, restrictions such as mask wearing, frequent hand washing, and social distancing will still be required for the next several months to slow the spread of the virus and flatten the curve.”

Accordingly, the good news about vaccination comes with a plea.

“Because we don’t see the immediate impact of our actions, it’s hard sometimes to understand that our behaviors make a difference,” McMahon said. “But they make a tremendous difference. By wearing your mask, social distancing, and, when it’s available, getting the vaccine, you can do a lot to protect yourself and others from getting sick.”

This article can be found at [At Los Alamos National Lab, Supercomputers Are Optimizing Vaccine Distribution (hpcwire.com)]

Distributing a highly anticipated new release: The COVID-19 vaccine

December 16, 2020

Most holiday seasons, discussion of urgent deliveries conjures images of UPS drivers rushing to doorways with Amazon packages, long lines at the post office, and Santa's sleigh landing on snow-topped roofs. Not this year. In December 2020, "urgent delivery" meant one thing: the COVID-19 vaccine rollout.

After months of anticipation, the vaccine has been delivered to every state in the nation, including New Mexico, which received its first shipments on Dec. 14. But vaccinating more than 250 million adults in the United States is a monumental task that requires careful planning and assessments of different approaches to distribution.

At Los Alamos, scientists are using mathematical models and computational simulations enabled by LANL's supercomputing capabilities to understand how best to distribute the COVID-19 vaccine to minimize impacts on the healthcare system and the overall population. This information can help decision makers determine which mitigation strategies to implement and how to safely reopen various parts of the community as the vaccine is rolled out.

To understand the different outcomes based on how the vaccine will be distributed, researchers are looking at various what-if scenarios.

For example, the model takes into account variables such as the percentage of the population that gets the vaccine, the vaccine's effectiveness, the different populations that will get the vaccine first (such as healthcare workers and seniors), school re-openings, business re-openings, etc. Each of these variables impacts how the disease will spread through a community. The model can also look at how the COVID-19 case and death rate, for example, will be affected if 60 percent of the population is vaccinated with a vaccine that is 90 percent effective and some parts of the community—such as schools and certain businesses—reopen.

"The first thing we looked at was whether it made a difference to prioritize certain populations—such as healthcare workers—or to just distribute the vaccine randomly," said Sara Del Valle, a computational epidemiologist and leader of the COVID-19 modeling team. "We learned that prioritizing healthcare workers first was more effective in reducing the number of COVID cases and deaths."

One of the things that sets LANL's models apart from others like them are their level of granularity. Unlike other models, those developed at LANL can drill down to the county level of every state in the nation. By incorporating explicit information at the county level, such as demographics (age, gender, household size) and even different industries in which people work (healthcare, education, public transportation, etc.), it can give a clearer picture of the impact of the vaccine on a community and different populations within that community.

The various scenarios that the models run were developed in collaboration with local, state, and federal government officials as they effectively plan for vaccine distribution and complementary mitigation strategies.

“These models very clearly illustrate that, for many months, the vaccine alone isn’t going to be enough to keep us safe,” said Ben McMahon, also a mathematical epidemiologist who heads up LANL’s part of the DOE’s multi-lab National Virtual Biotechnology Laboratory modeling effort to tackle COVID-19. “Given the limited vaccine supply and the fact that immunity builds steadily for several weeks after vaccination, restrictions such as mask wearing, frequent hand washing, and social distancing will still be required for the next several months to slow the spread of the virus and flatten the curve.”

Both Del Valle and McMahon stress that every person has an important role to play in slowing the disease’s spread. “Because we don’t see the immediate impact of our actions, it’s hard sometimes to understand that our behaviors make a difference,” said McMahon. “But they make a tremendous difference. By wearing your mask, social distancing, and, when it’s available, getting the vaccine, you can do a lot to protect yourself and others from getting sick.”

The models also show that it will be several more months before things start to return to some semblance of “normal,” but, as Del Valle said, “There’s a light at the end of the tunnel.” And that, for most everyone, is the most anticipated and welcomed gift the holiday season.

LA-UR-20-30256

https://www.santafenewmexican.com/opinion/commentary/covid-19-vaccine-critical-but-its-not-silver-bullet/article_033e8b90-4f8e-11eb-83a3-133af6a2c895.html

COMMENTARY SARA DEL VALLE AND BEN MCMAHON

COVID-19 vaccine critical but it's not silver bullet

By Sara Del Valle and Ben McMahon
Jan 5, 2021

After months of anticipation, the COVID-19 vaccine has been delivered to every state in the nation and inoculations are underway. But vaccinating more than 250 million adults throughout the country is a monumental task that requires careful planning and assessments of different approaches to distribution — without which herd immunity can take longer to achieve.

At Los Alamos National Laboratory, we're using mathematical models and computational simulations enabled by the laboratory's supercomputing capabilities to understand how best to distribute the COVID-19 vaccine. And what we've learned is: While the vaccine is a critical weapon in fighting this virus, it's not a silver bullet — at least not yet.

Our models look at individual communities based on government data. To understand the different outcomes based on how the vaccine will be distributed, we create various what-if scenarios that were developed in collaboration with local, state and federal governments to help them effectively plan for vaccine distribution and complementary mitigation strategies.

Our models can drill down to the county level by incorporating explicit demographics (age, gender, household size, etc.) and even different industries in which people work. This level of granularity — something unique to our models — gives us a clearer picture of the impact of the vaccine on a community and different populations within that community.

We ran multiple simulations based on various scenarios, including vaccine effectiveness, allocation, and prioritized. We also simulated the percentage of people willing to get vaccinated, which will have a significant impact on the spread of the disease. Based on surveys of adults, 40 percent to 60 percent have said they are willing to get the vaccine, so we simulated the outcome based on that range. We also factored in variables such as school attendance, mobility data and public interactions in various businesses.

So when we did all this, what did we learn?

Consistently, these models illustrate that, for many months, the vaccine alone isn't going to be enough to keep us safe. Due to the limited vaccine supply and the fact that immunity builds steadily for several weeks after vaccination, our models show that continuing to limit business activity will allow communities to flatten the curve and subsequently increase the potential impact of the vaccine.

Furthermore, they show that opening schools at full capacity can increase the risk of COVID-19 spread, while the hybrid-learning scenario (40 percent of students go to school in person for two days and the other 40 percent go the other two days) in combination with limited business activity reduces risk, enables in-person education and increases the impact of the vaccine by flattening the curve.

Our models are not foolproof. Being able to account for uncertainties in people's behaviors and the spread of a new pathogen in a complex model is extremely challenging — and something we spend significant time trying to understand. But the models are still valuable in helping us to quantify the potential outcomes of different what-if scenarios.

And what they show us is that it's critical for everyone to recognize the important role they play in slowing the disease's spread. Because we don't often see the immediate impact of our actions, it's hard sometimes to understand that individual behaviors make a difference. But they do. By wearing masks, social distancing and, when it's available, getting the vaccine, we all can do a tremendous amount to protect ourselves and others and keep the virus at bay.

Sara Del Valle is a mathematical epidemiologist and leader of the COVID-19 modeling team at Los Alamos National Laboratory. Ben McMahon is a mathematical epidemiologist who heads up Los Alamos' part of the Department of Energy's National Virtual Biotechnology Laboratory modeling effort to tackle COVID-19.

Assessing The Impact of Vaccine Distribution Strategies Using an Agent-Based Model

Preliminary Results

WHO SAGE Working Group on COVID-19 Vaccines

Timothy Germann, Lori Dauelsberg, Manhong Zhu Smith, Geoffrey Fairchild, Morgan Gorris, Terece Turton, Carrie Manore, and Sara Del Valle

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December 21, 2020

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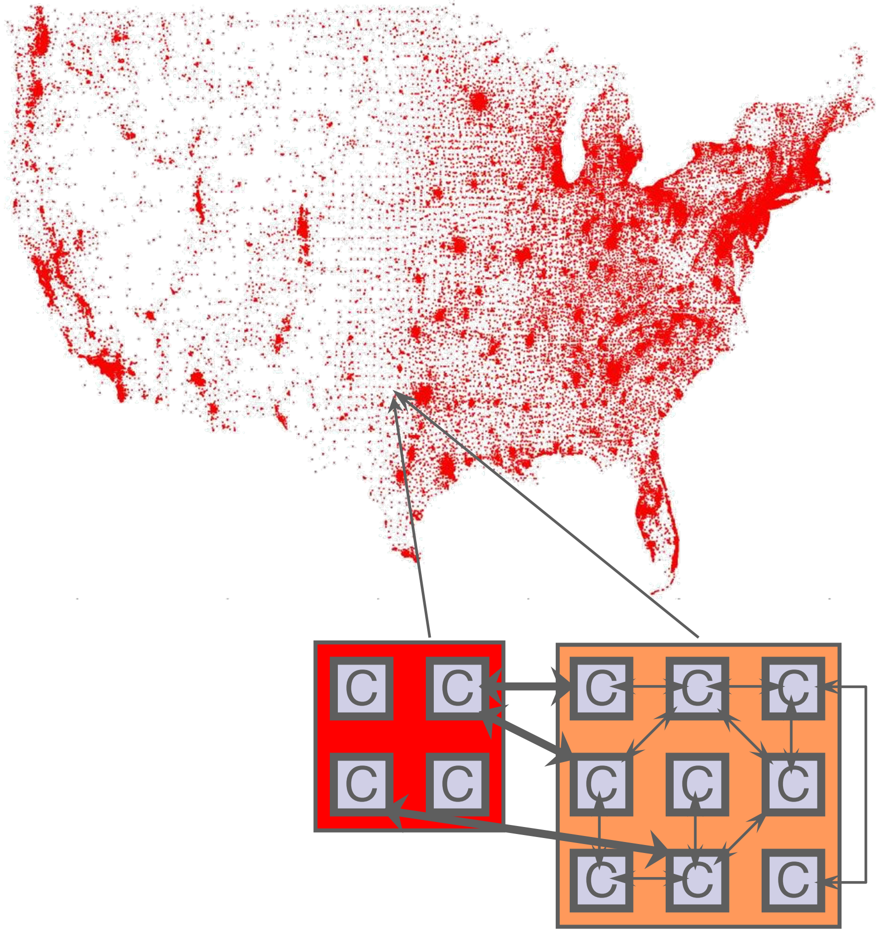
LA-UR-20-3071

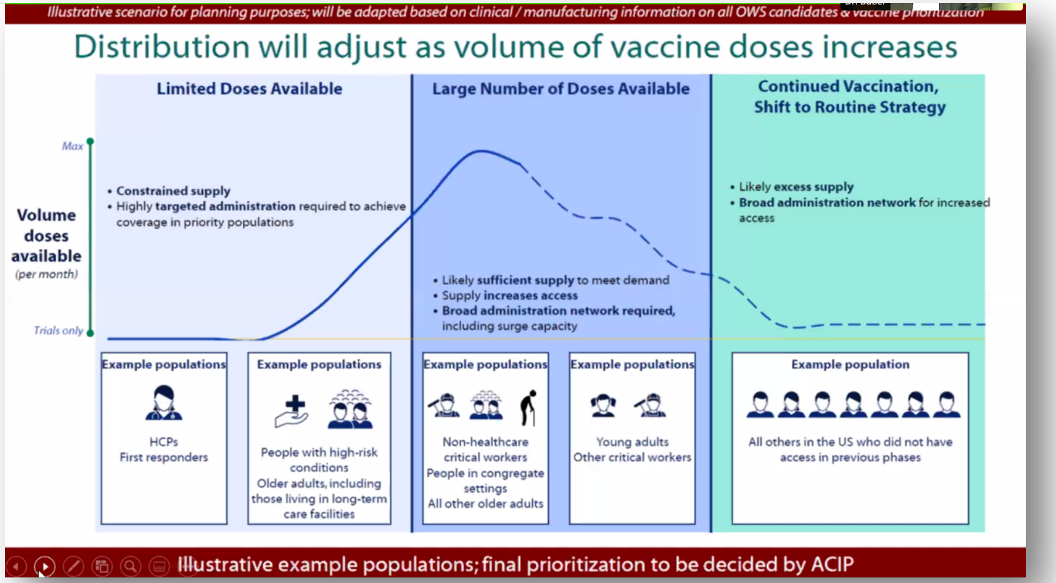
EpiCast Overview

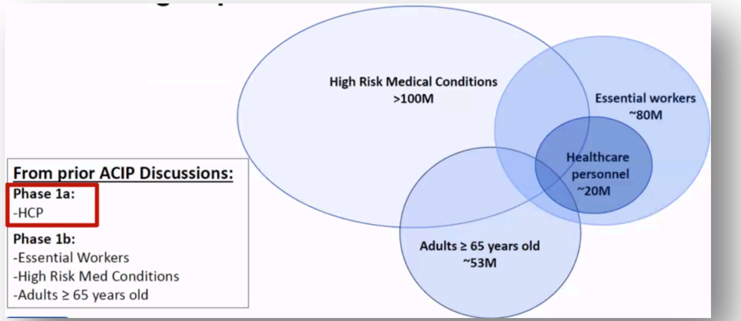
- An agent-based model used to simulate the spread of disease throughout the U.S. population
  - 2000-person communities in 65,433 census tracts
  - Explicit model of geography, demographics (i.e., age), worker/household/school/ community contacts, and mitigations
  - Captures **workforce by 3-digit NAICS**
- Data sources
  - U.S. Census Data
  - U.S. Department of Transportation
  - STP64 Commuter Data



Vaccine Modeling Assumptions

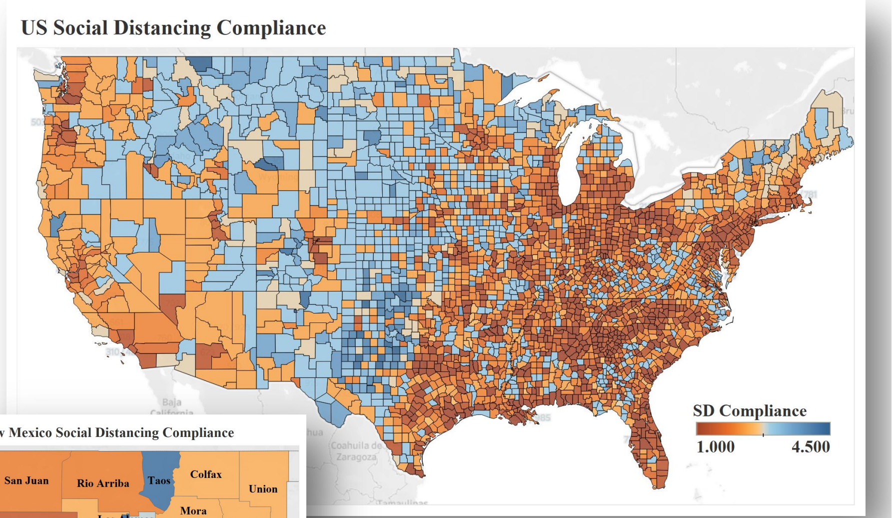
- **Vaccine Effectiveness**
  - 75% and **90%** (after 4 weeks)
- **Vaccine Allocation for NM -> U.S. (starting mid December)**
  - December: 112k (70k Pfizer & 42k Moderna) -> 40M
  - January: 290k (174k Pfizer & 116k Moderna) -> 50M
  - Feb – Mar: 348k/month (203k Pfizer & 145k Moderna) -> 60M/month
- **Prioritization Groups for the U.S.**
  - 1a:Healthcare workers; 1b: essential workers; 1c: 65+
- **Percent of Population Willing to Get Vaccinated**
  - **40%** and 60% (only 16+) – **conservative assumption**
- **Childhood Reduced Transmission Assumptions**
  - 30% in children K-12
- **Initial Conditions & Model Calibration**
  - First 10 days in December

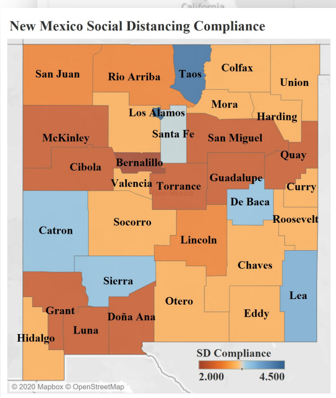




Modeling Assumptions

- **Schools**
  - **100%** open 5-days/week, **80%** attendance 5-days/week, **hybrid** (two non-overlapping cohorts of 40% each attending school 2-days/week), **closed** (virtual learning)
  - Social distancing compliance is based on unacast scores (see below)
- **Social Distancing Compliance**
  - Unacast scores (mobility data) at the county level -> **Blue** (higher compliance); **dark orange** (lower compliance)
  - All scenarios assume reduction in contacts due to social distancing and facemask mitigations implemented in all settings (e.g., school, work, neighborhood)
- **Limitations**
  - We don't take the winter holiday into account -> overestimating school transmission/underestimating spread from holiday gatherings





	Working Status				Reduction in Contacts due to social Distancing		Long Distance Travel
Workplace Assumption	Full Time	Part-time or Shift	Telework Take-up	Laid Off	Workplace	Other non-household	
Fewer Open Workplaces	44%	32%	20%	16%	10%	50%	50%
More Open Workplaces	52%	32%	15%	8%	10%	25%	75%

Modeling Assumptions Cont.

- **Workplaces**
  - Essential/non-essential businesses (based on industry classification) and approximate compliance based on Public Health Orders
  - Phase 2: Fewer workplaces open (red)
  - Phase 3: More workplaces open (yellow/green)
  - Public interactions in businesses differentiated by "necessity" by industry(highest in retail, lowest in construction)

NAICS Sector	NAICS 2-Digit Code	Ability to Telework (Median)
Agriculture & Mining	11	8.1%
Utilities & Construction	21-23	32.7%
Manufacturing	31-33	41.0%
Wholesale	42	26.5%
Retail	44-45	26.5%
Transportation & Warehousing	48-49	32.7%
Information	51-52	80.4%
Finance, Insurance, & Real Estate	52-53	81.1%
Professional and Business Services	54-56	71.6%
Education	61	47.9%
Health & Social Services	62	47.9%
Leisure & Hospitality	71-72	20.3%
Other Services	81	39.9%
Government & Administration	92	57.0%

NAICS Sectors Employess Working Onsite by Sector

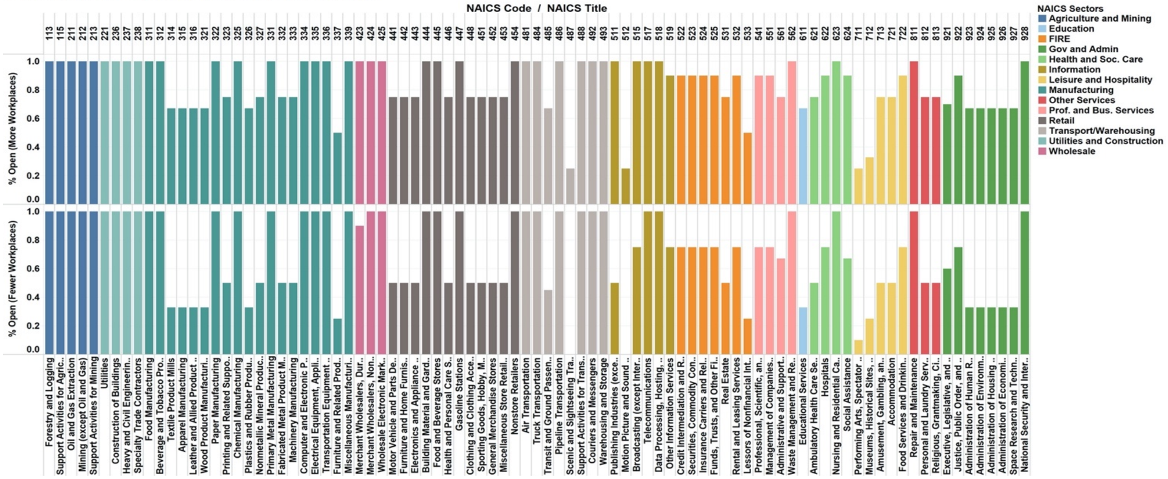
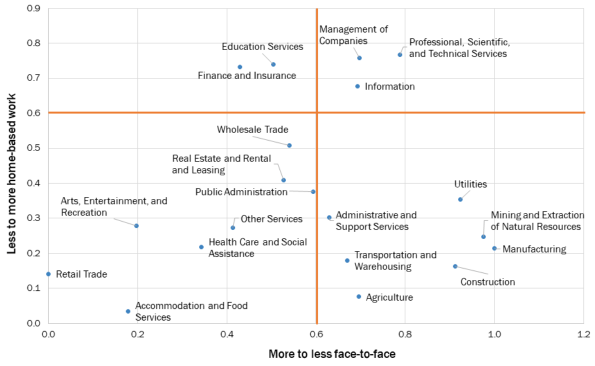


Figure 1. Home-based work and face-to-face interactions don't always go hand-in-hand



Source: Authors' calculations based on Dingel and Neiman (2020) and the O*NET database. BROOKINGS

School Scenarios Description & Assumptions

Virtual Learning (Schools Closed)

- All **household contacts** are increased by 40%
- **Daycares** are assumed to be open
- **School-age children are assumed to mix with other children within their neighborhood** at a reduced rate
- Neighborhood transmission is reduced by **50% or 25% (depending on Phase 2 or 3, respectively)** to account for social distancing measures and facemasks

Hybrid Learning (Schools Open)

- Students are stratified into **two non-overlapping** groups of 40% each
- Students are assumed to go to school for **only 2 days a week or alternating weeks** under social distancing restrictions
- School-age children are assumed to mix with other children within their neighborhood at a reduced rate
- School transmission is reduced by **50% or 25% (depending on Phase 2 or 3, respectively)** to account for social distancing measures, facemasks, mixing groups, etc.

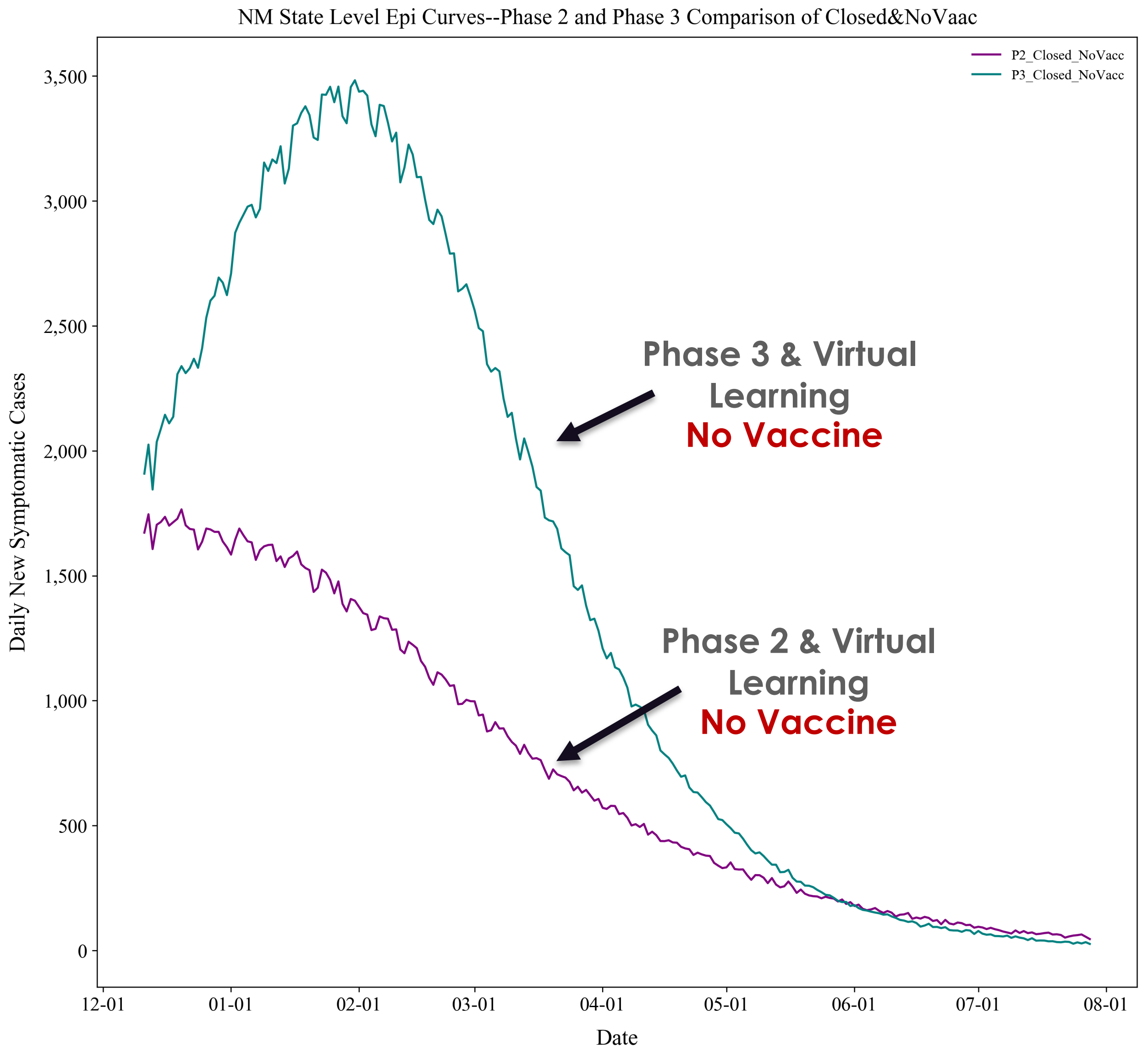
Full or 80% Onsite Learning (Schools Open)

- Schools are assumed to be opened **5 days a week**
- Either 100% or 80% of the student population is assumed to attend in person (80% assumption due to surveys indicating 20% of parents may not send their children back to school)
- School transmission is reduced by **50% or 25% (depending on Phase 2 or 3, respectively)** to account for social distancing measures, facemasks, mixing groups, etc.

> NM Preliminary Results

Most results shown are for the state of New Mexico unless otherwise stated.

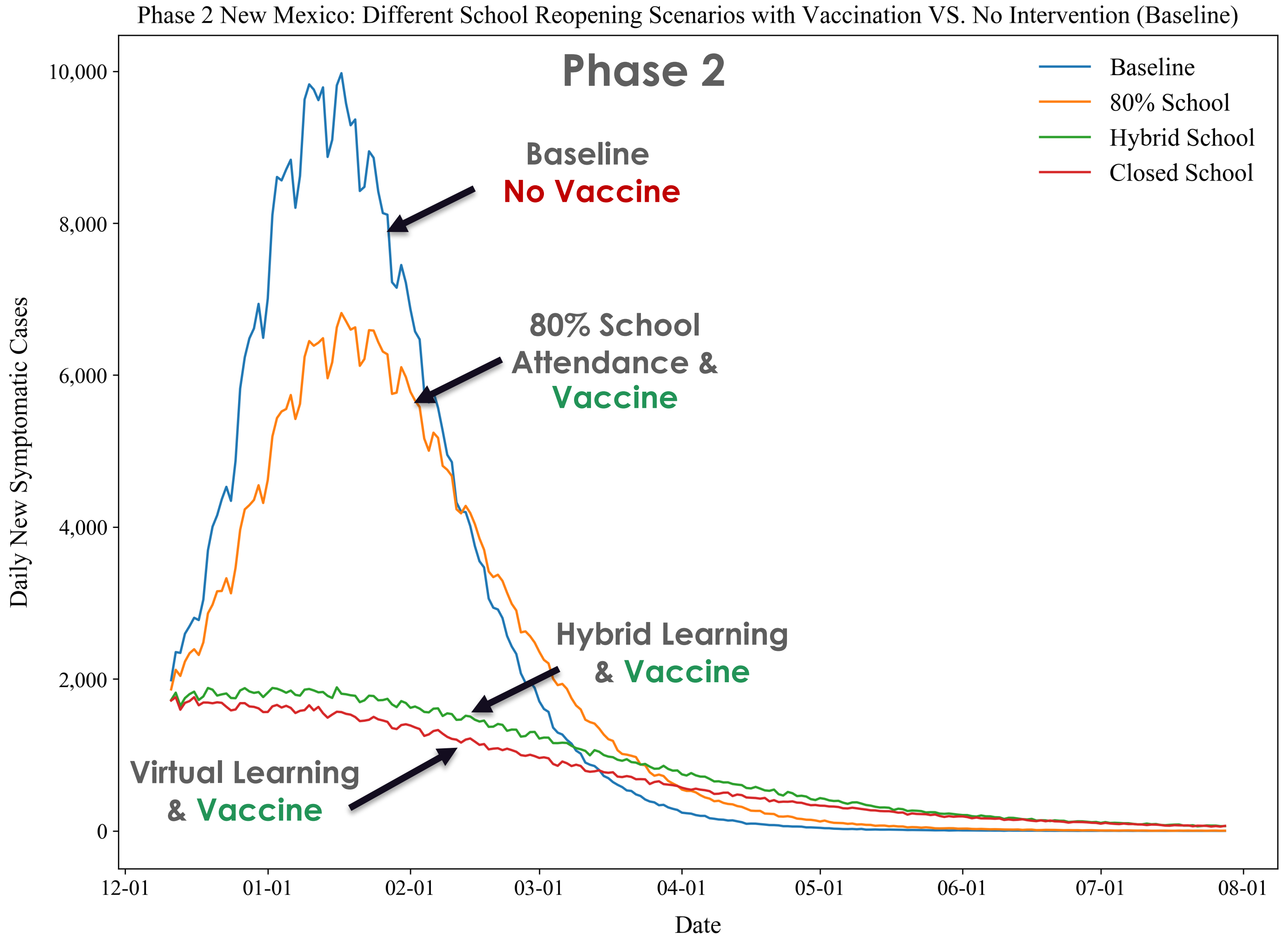
NM: Impact of Business Activity (Phase 2 vs. Phase 3)



So what?

- Even if schools implement virtual learning, the level of business activity will impact disease spread
- Limited business activity (Phase 2) reduces social contacts, which in turn reduce overall risk of infection and cases
- Clinical Attack Rate
  - Phase 2: 11%
  - Phase 3: 21%

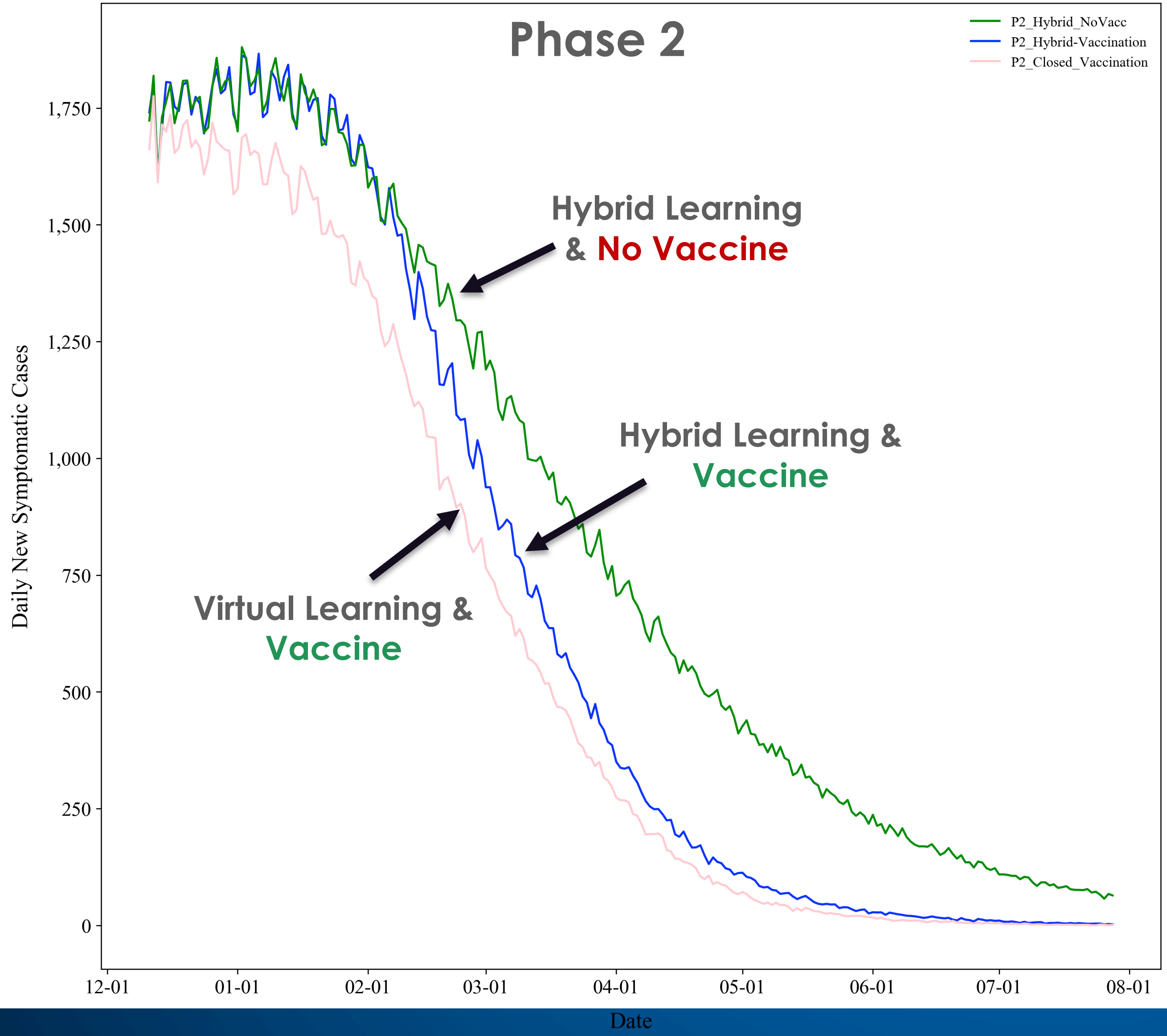
NM: Impact of Vaccine & School Options (Phase 2)



So what?

- The Phase 2 baseline scenario corresponds to limited business activity, 100% school attendance, and vaccine distribution starting mid December
- The vaccine will have limited impact, if schools reopen at 80% or 100% attendance levels while in Phase 2
- The hybrid and virtual learning scenarios significantly reduce disease spread and increase the impact of the vaccine
- Clinical Attack Rate
  - Baseline (no vaccine): 32%
  - 80% School (vaccine): 27%
  - Hybrid (vaccine): 13%
  - Virtual (vaccine): 11%

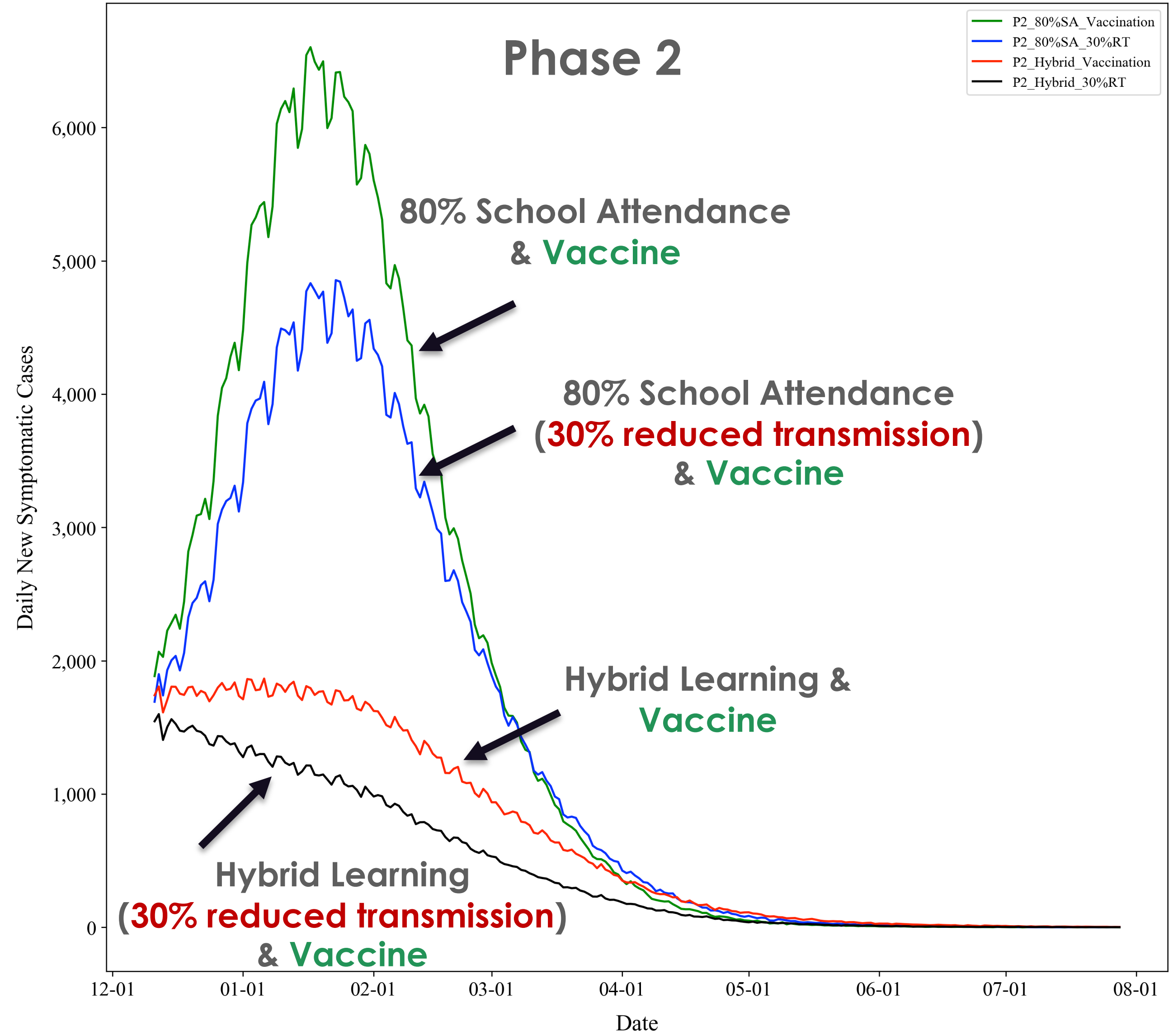
NM: Impact of Vaccine & School Options (Phase 2)



So what?

- Phase 2 (limited business activity) can help reduce disease spread, even in the absence of vaccine
- Hybrid learning in combination with vaccine reduces risk while enabling in-person education
- Virtual learning, while it reduces cases, it doesn't offer a significant impact when compared to hybrid learning
- The impact of vaccination can be seen starting February

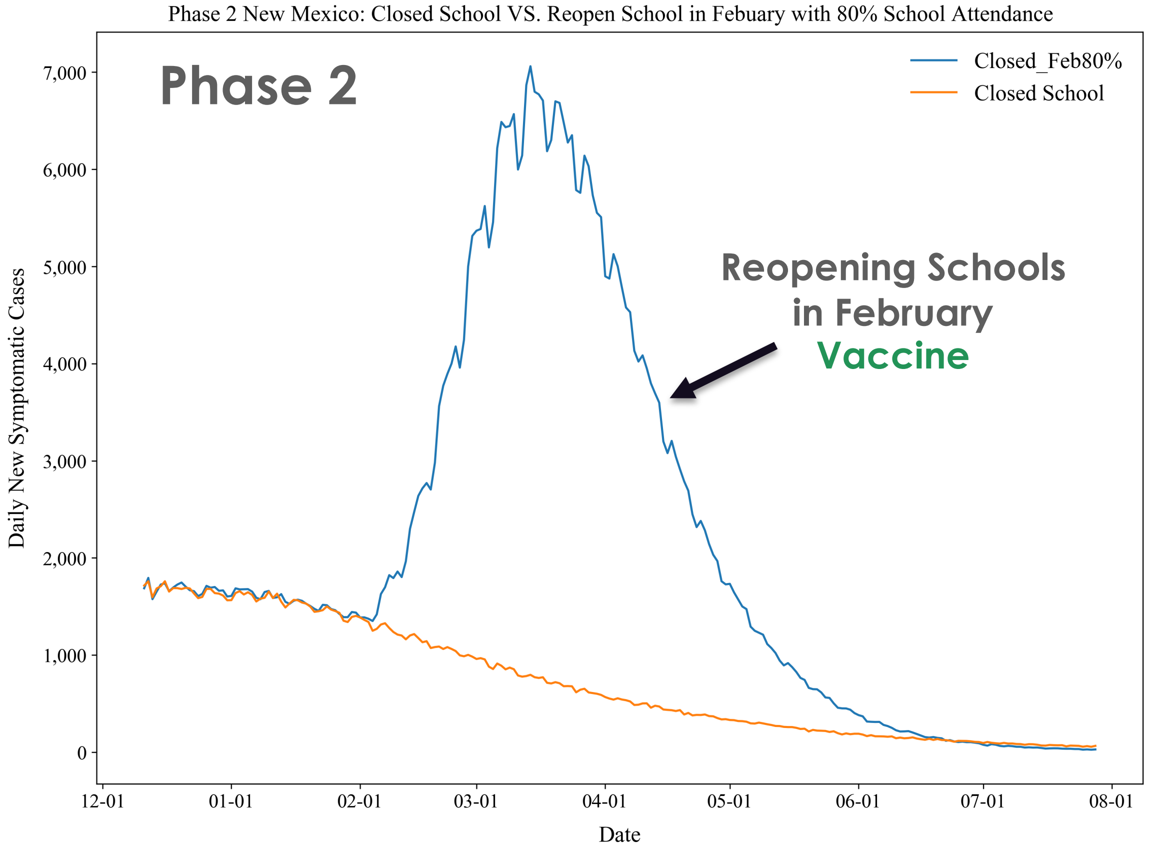
NM: Impact of Reduced K-12 Transmission (30%)

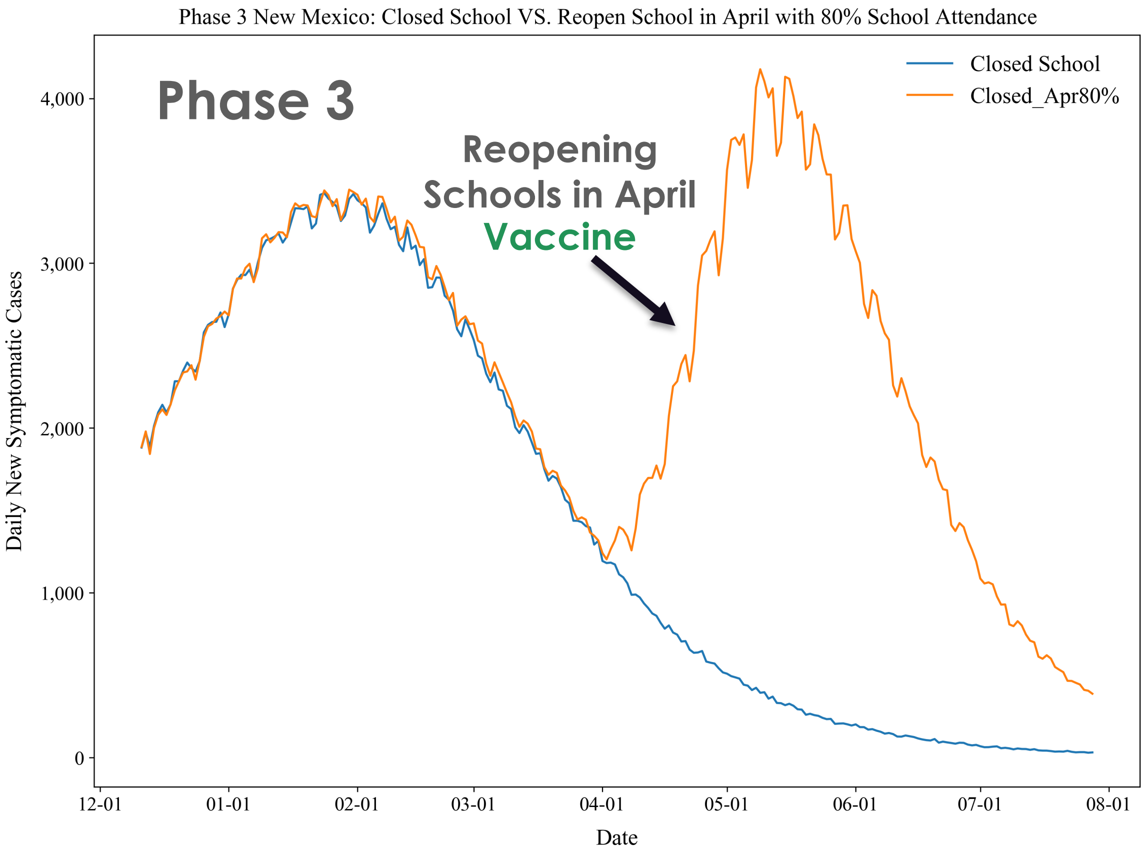


So what?

- Reduced transmission in K-12 children reduces the clinical attack rate from 23% to 21% (80% scenario) and from 9% to 7% (hybrid scenario)
- Opening the schools at 80% capacity, even under reduced transmission among K-12 children, can lead to significant spread
- The hybrid learning scenario can flatten the curve by reducing spread and increasing the potential impact of the vaccine

NM: When Can We Reopen Schools at 80% Post Virtual?

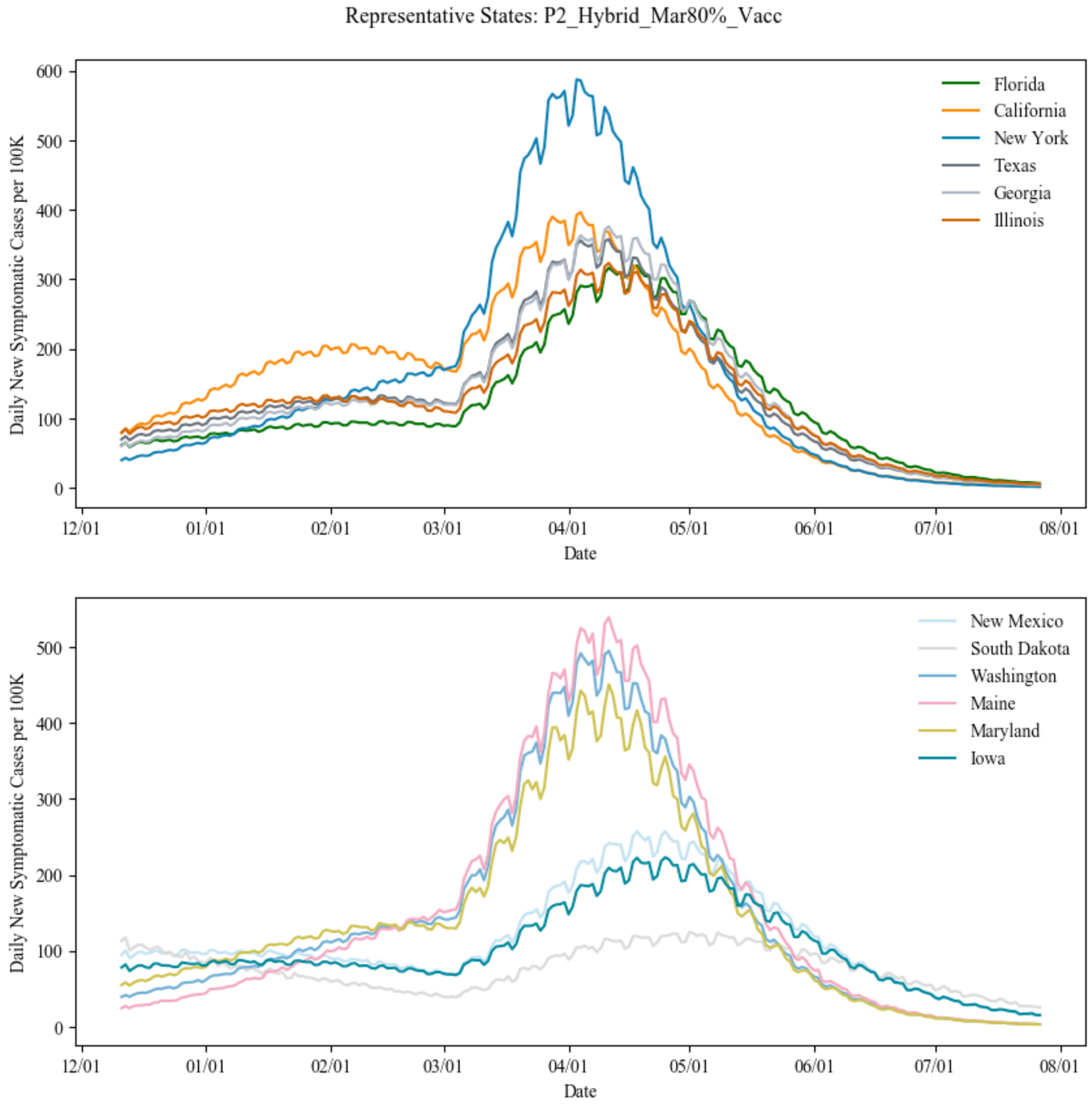




So what?

- **Reopening schools (post virtual learning) at 80% capacity in either February (Phase 2) or April (Phase 3) can lead to secondary waves of infection**
- **Given the limited vaccine supply and the time it takes to develop immunity, additional restrictions will be needed to reduce spread and increase the impact of the vaccine**

U.S. Phase 2: Impacts of Vaccination and Reopening Schools for 12 States



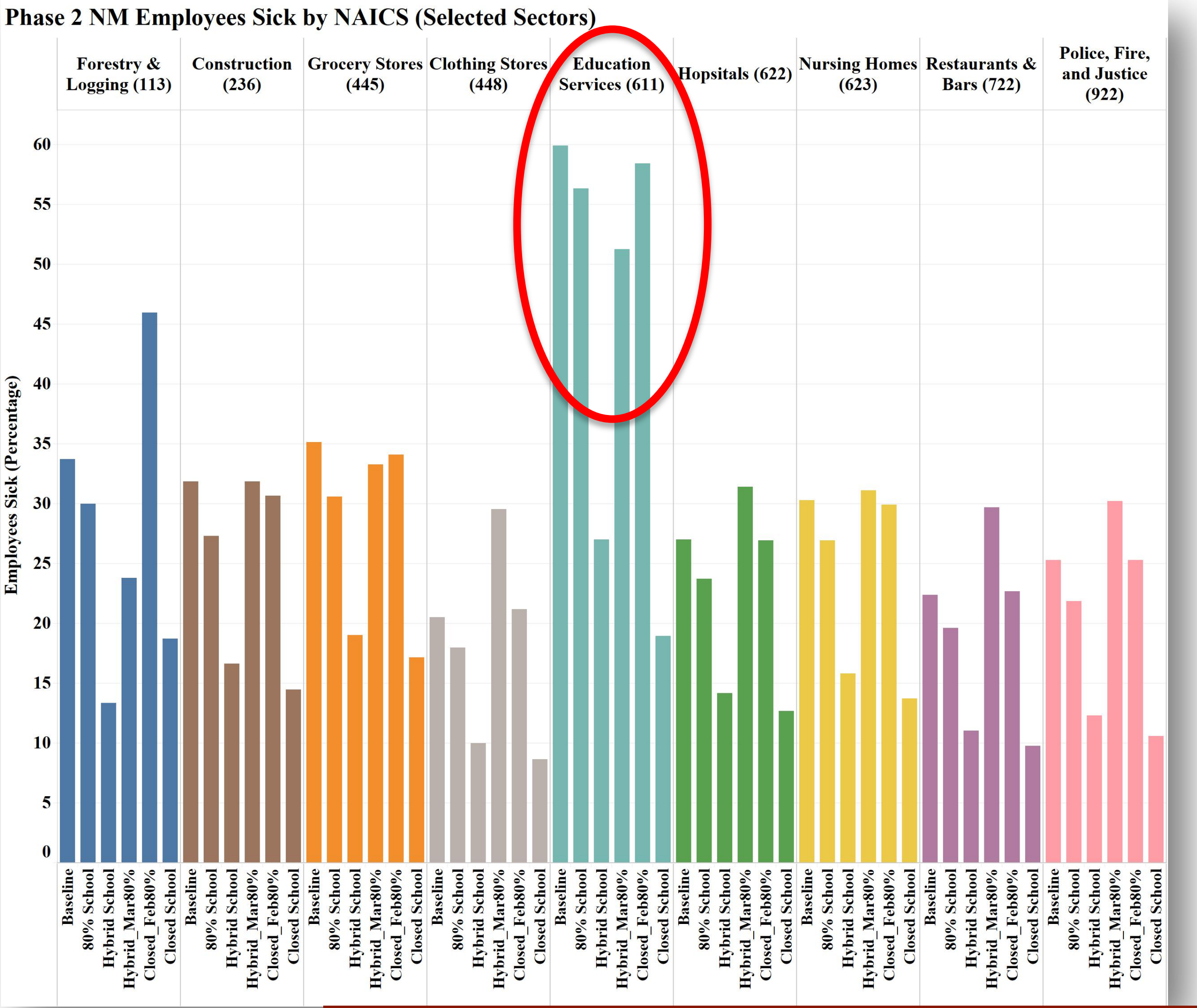
So what?

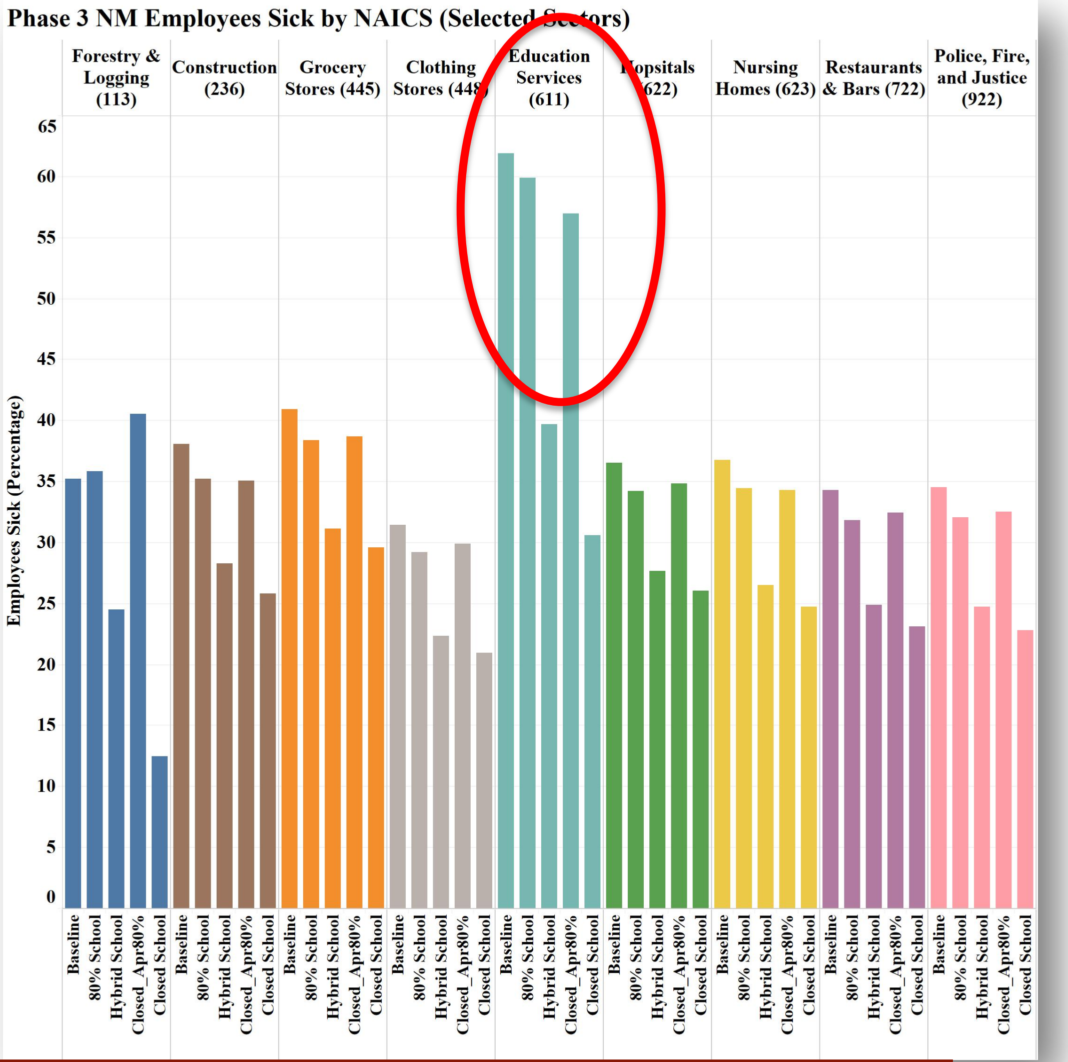
- What happens if schools move from hybrid learning to 80% attendance 5-days a week starting <u>March 1st</u>

- Spatial differentiation for 12 representative states is evident as a result of local trends and demographics

- Reopening schools 5 days a week at 80% capacity is likely to lead to secondary waves of infection

NM: Impacts by Industry (Phase 2 vs Phase 3)

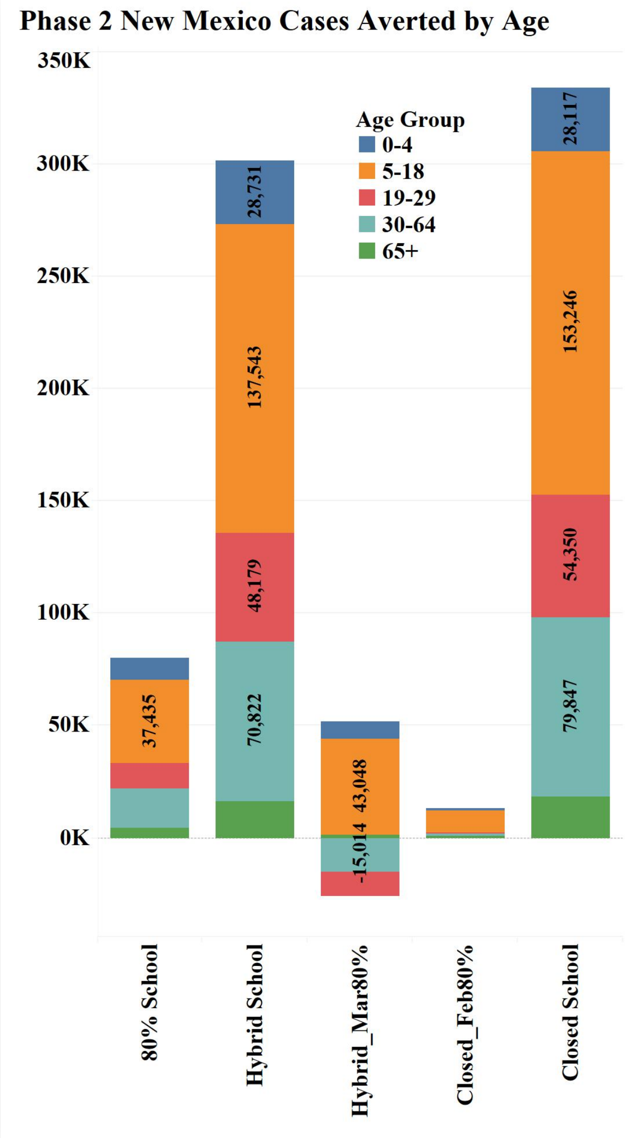


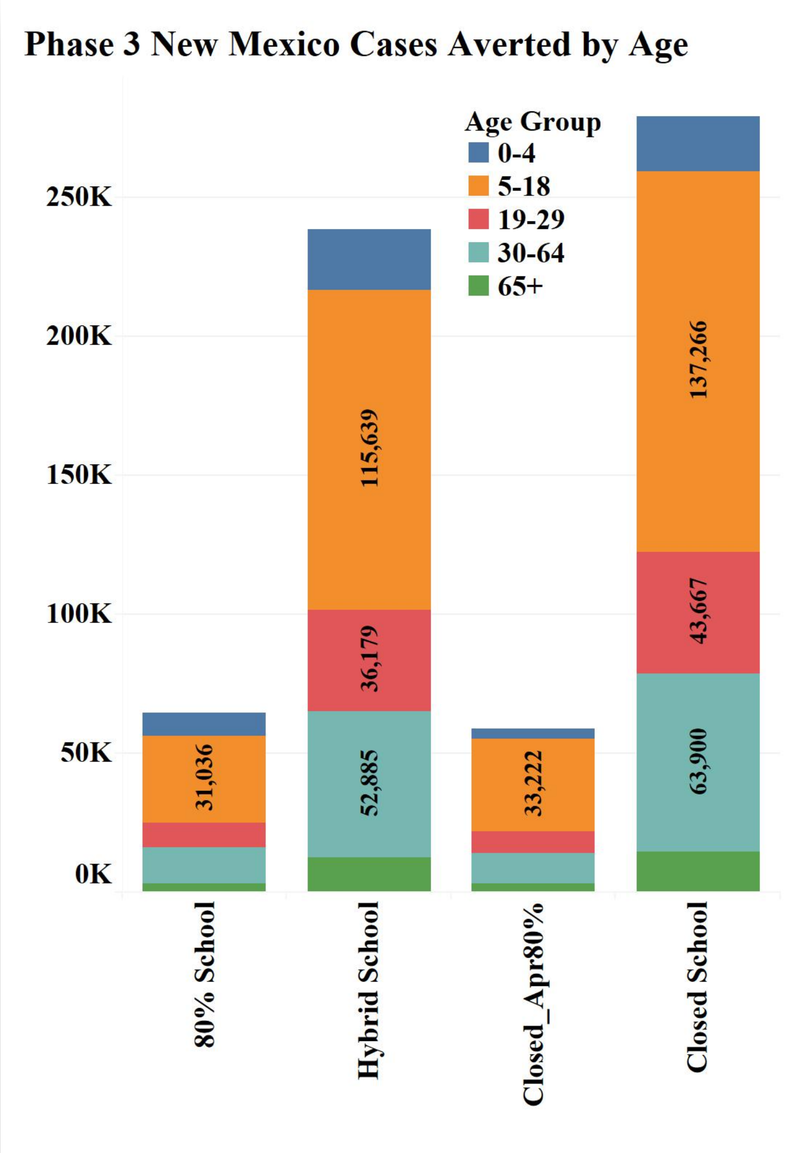


So what?

Reopening K-12 full time at full or 80% capacity before vaccine is fully rolled out puts educators at higher risk than many sectors

NM: Cases Averted (Phase 2 vs Phase 3)

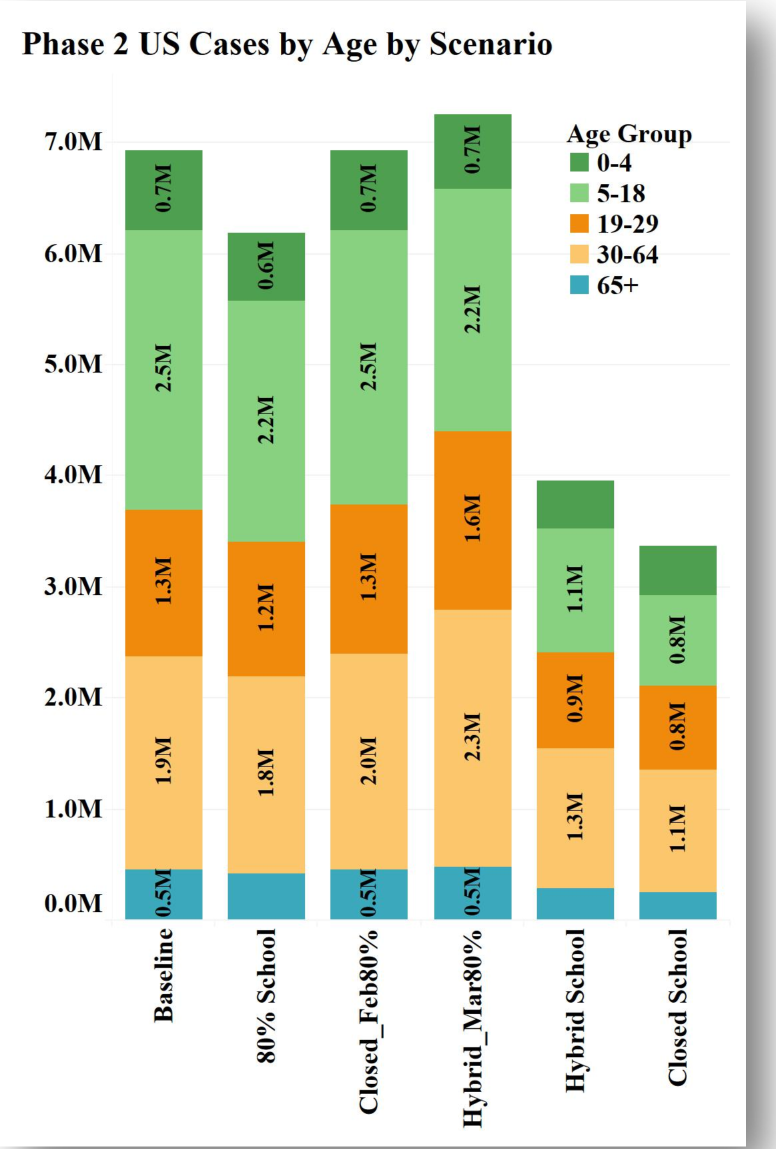


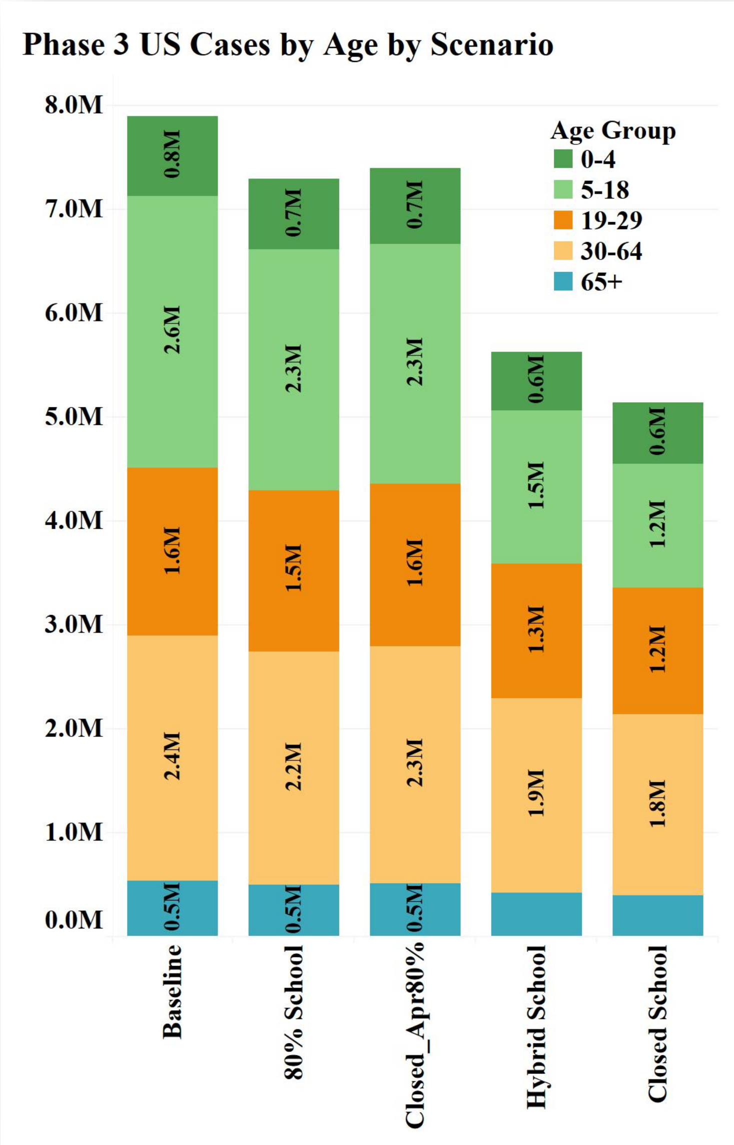


So what?

- Limited business activity (Phase 2) and hybrid school avert significant number of cases (~300K for NM)
- Limited business activity (Phase 2) in combination with virtual learning averts the most cases with over 325K cases averted
- Increased business activity (Phase 3) leads to fewer averted cases (240K hybrid and nearly 300K virtual)
- Reopening the schools and increasing business activity too early can have a negative impact by resulting in negative cases averted in two age groups (19-29 and 30-64)

U.S.: Cases by Age (Phase 2 vs Phase 3)

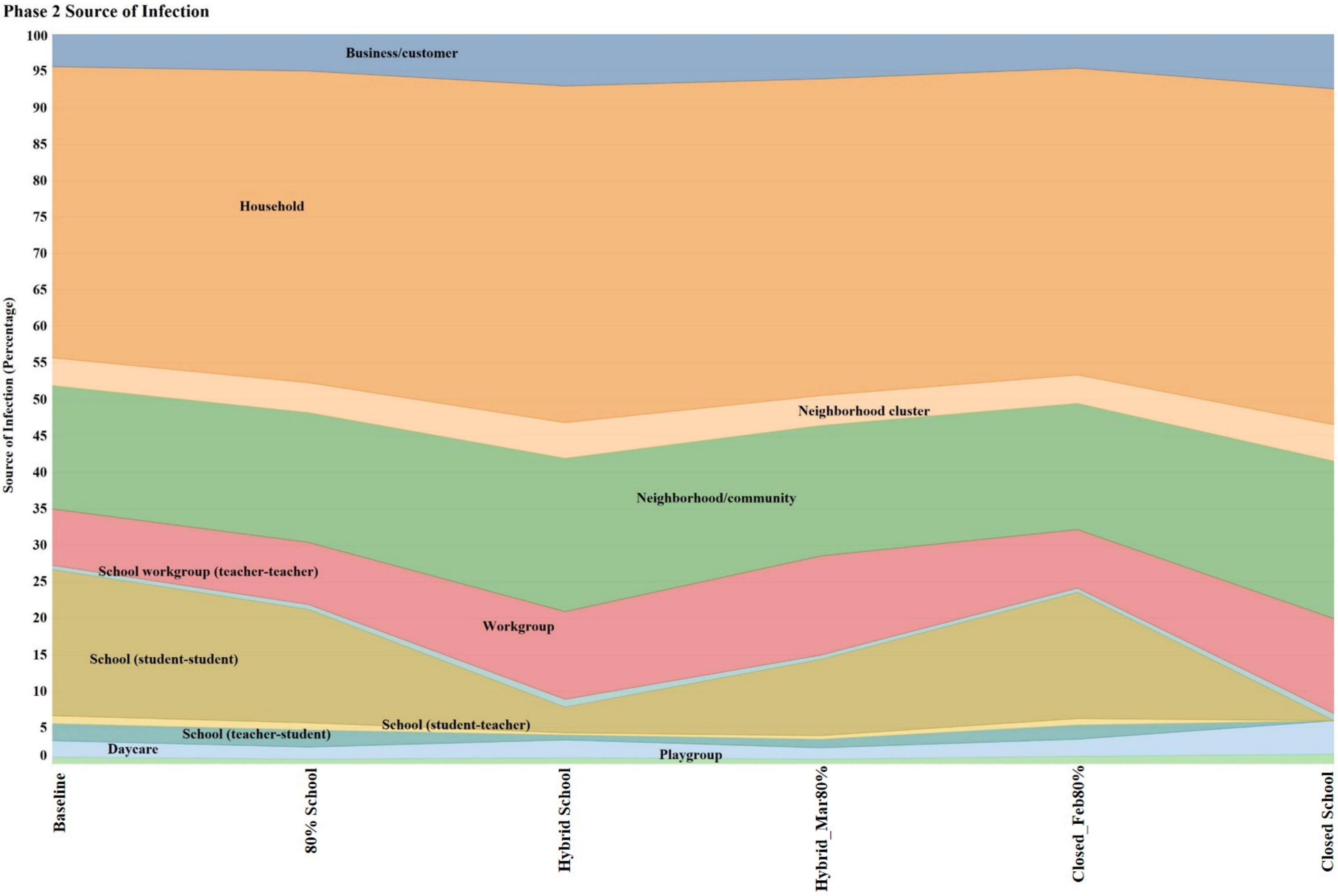




So what?

- The 0-18 age group will have the most cases across all scenarios followed by 30-64 age group

U.S.: Source of Infection (Phase 2)



So what?

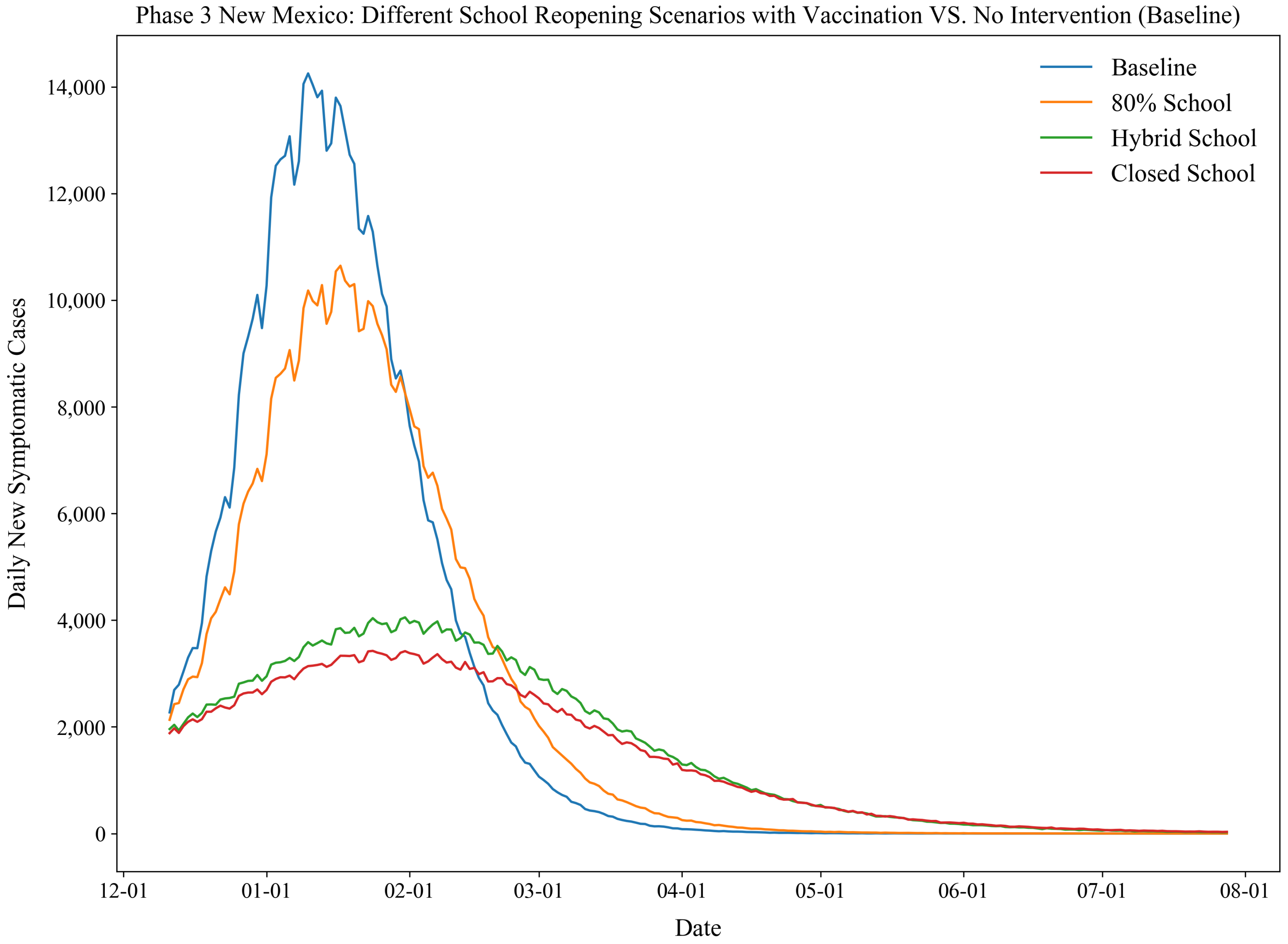
- The majority of cases are generated at home (37% - 46%) followed by neighborhood/community /cluster (20% - 27%)
- Schools generate between 3.5% (hybrid) to 20% (100% open) of the infections
- Workplaces generate between 8% and 14%

Conclusions our Study Supports

- Limited business activity (Phase 2) will allow us to **flatten the curve** and subsequently increase the potential impact of the vaccine
- 80% school attendance, even in the presence of reduced business activity (Phase 2) **can significantly increase disease spread**
- **Reduced transmission among children does not offer significant protection** if the schools open at 80% capacity
- The **hybrid learning scenario** (two non-overlapping cohorts of 40% each) provides the most balanced approach in terms of **reducing risk, enabling in-person education, and increasing the impact of the vaccine by flattening the curve**
- The **virtual learning scenario has the potential to avert the most number of cases** but the impact is limited when compared to the hybrid scenario
- Given the limited vaccine supply and amount it takes to develop protection, **reopening schools at 80% capacity 5-days per week can lead to secondary waves of infection**
- **School staff appears to have the highest risk of infection** when compared to other industries due to increased exposure to a non-vaccinated population (K-12)

> Additional Slides

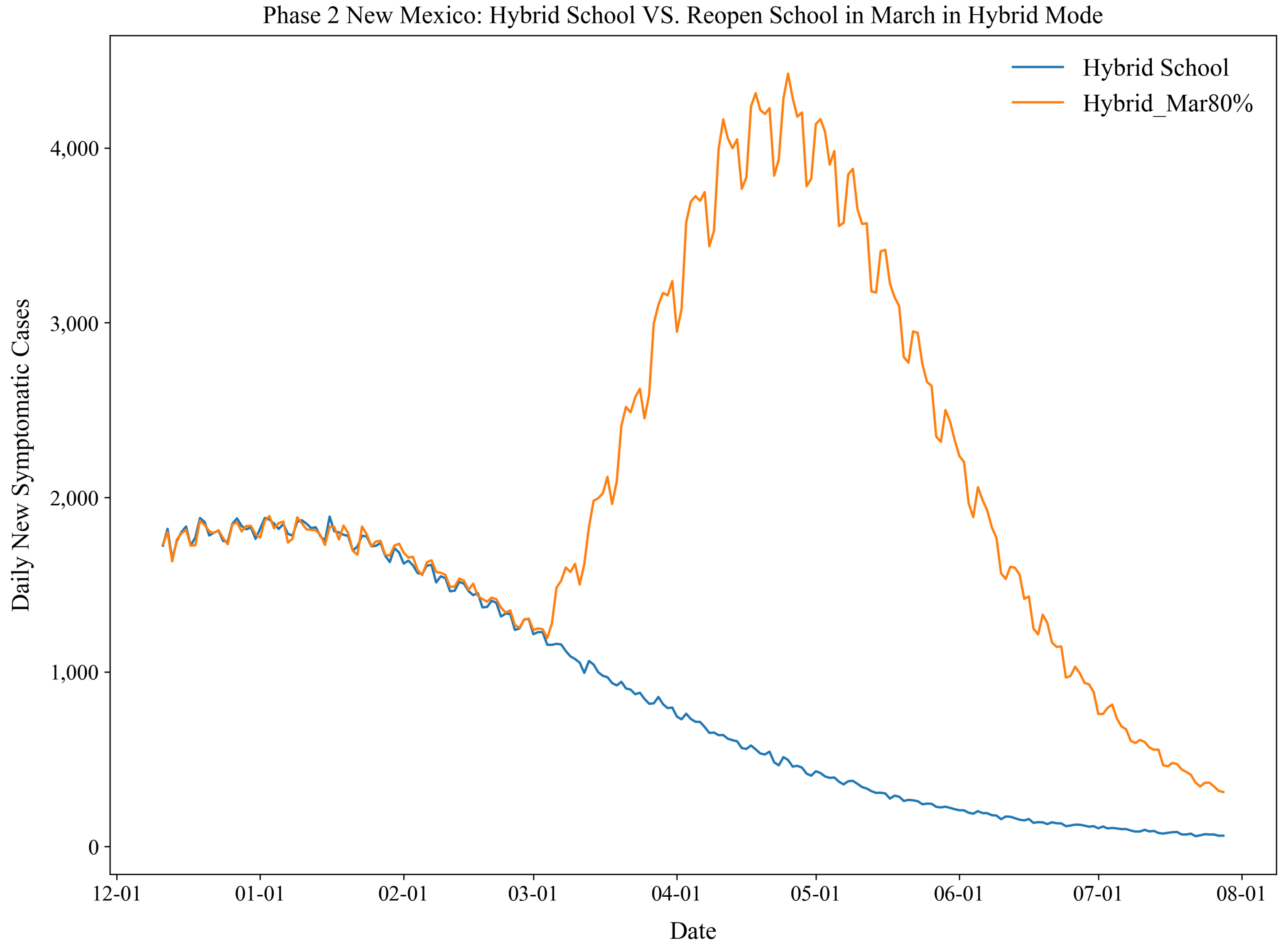
Impact of Vaccine & School Options (Phase 3)



So what?

- **The phase 3 baseline scenario corresponds to increased business activity, 100% school attendance, and vaccine distribution starting mid December**
- **The Phase 3 scenarios lead to increased number of cases when compared to Phase 2 scenarios**
- **The vaccine will have limited impact if schools reopen at 80% or 100% attendance levels while in Phase 3**

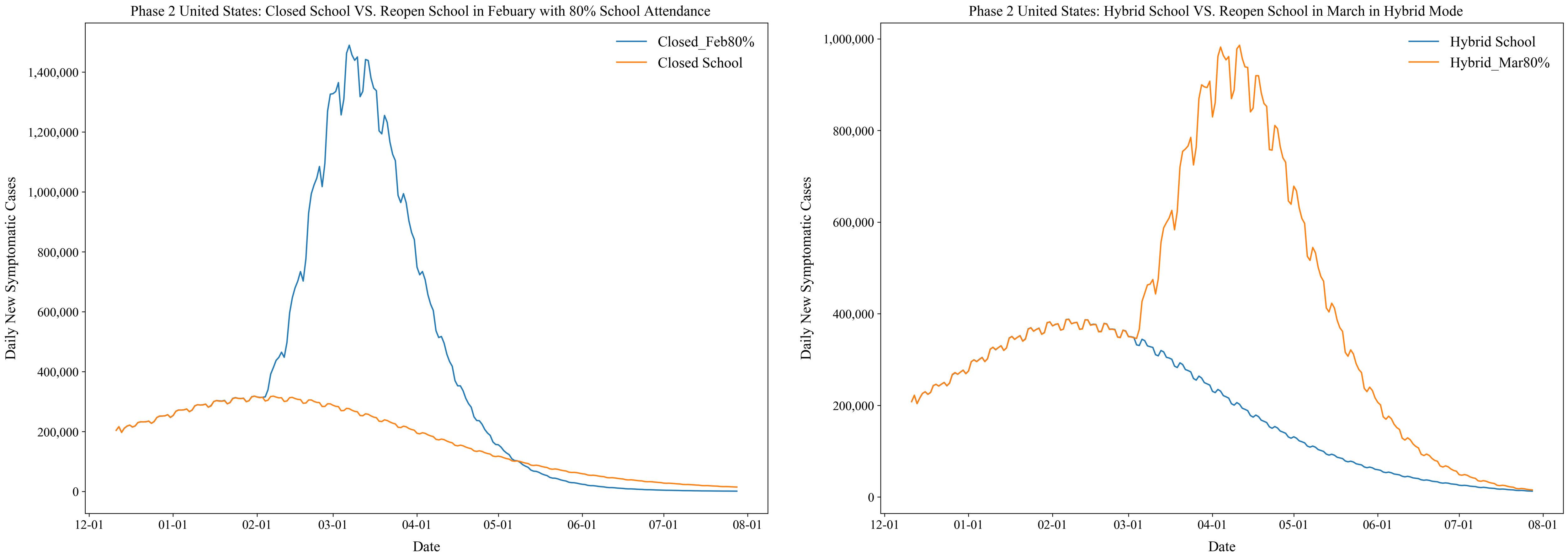
When Can We Reopen Schools at 80% Post **Hybrid**?



So what?

- Reopening schools (post hybrid learning) at 80% capacity in March (Phase 2) can lead to secondary waves of infection
- Given the limited vaccine supply and the time it takes to develop immunity, additional restrictions will be needed to reduce spread and increase the impact of the vaccine

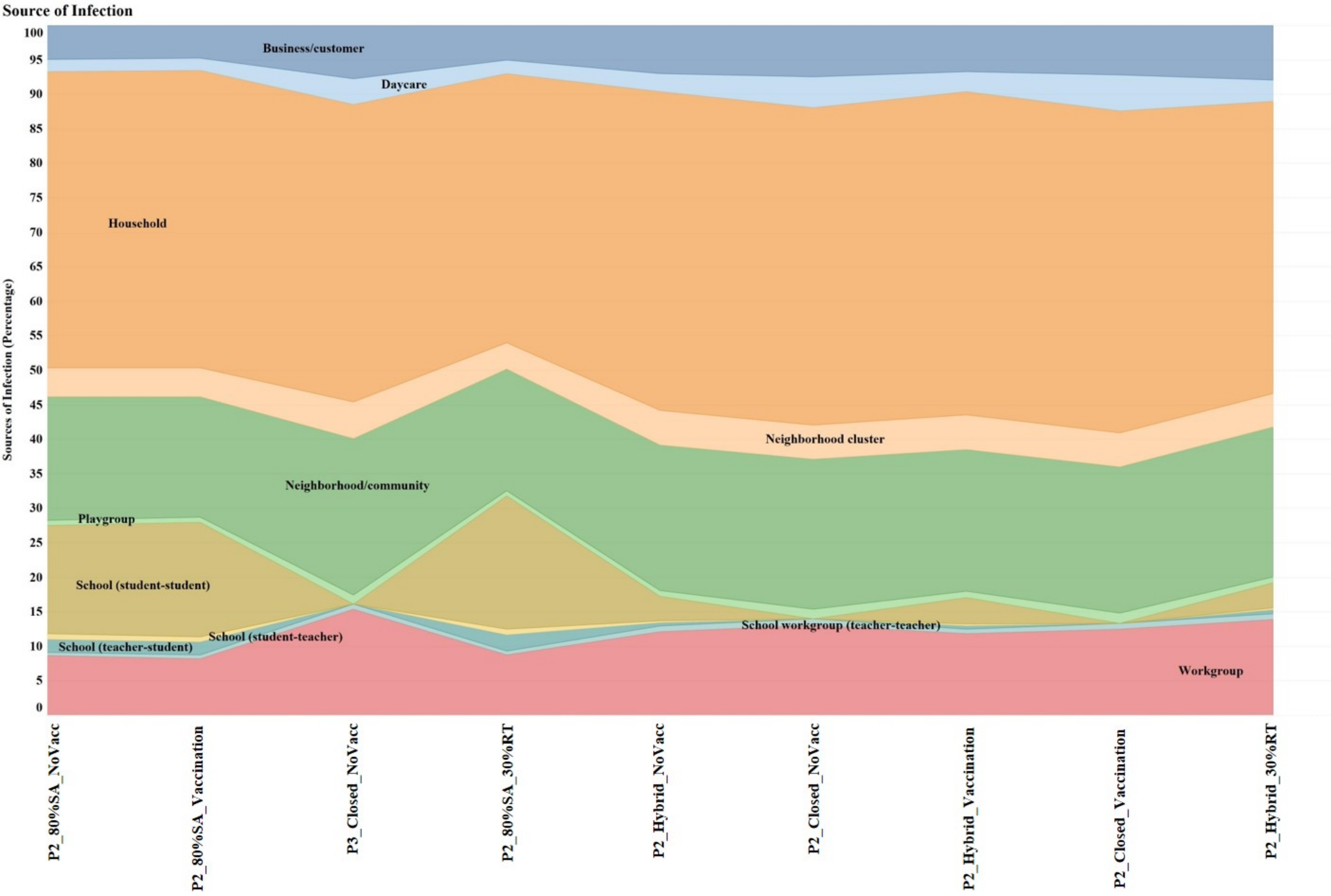
When Can We Reopen Schools at 80% Post Hybrid – U.S. Overall Impacts?



So What?

Secondary waves of infection are likely across the U.S. if the schools reopen too soon (before herd immunity is achieved through vaccination)

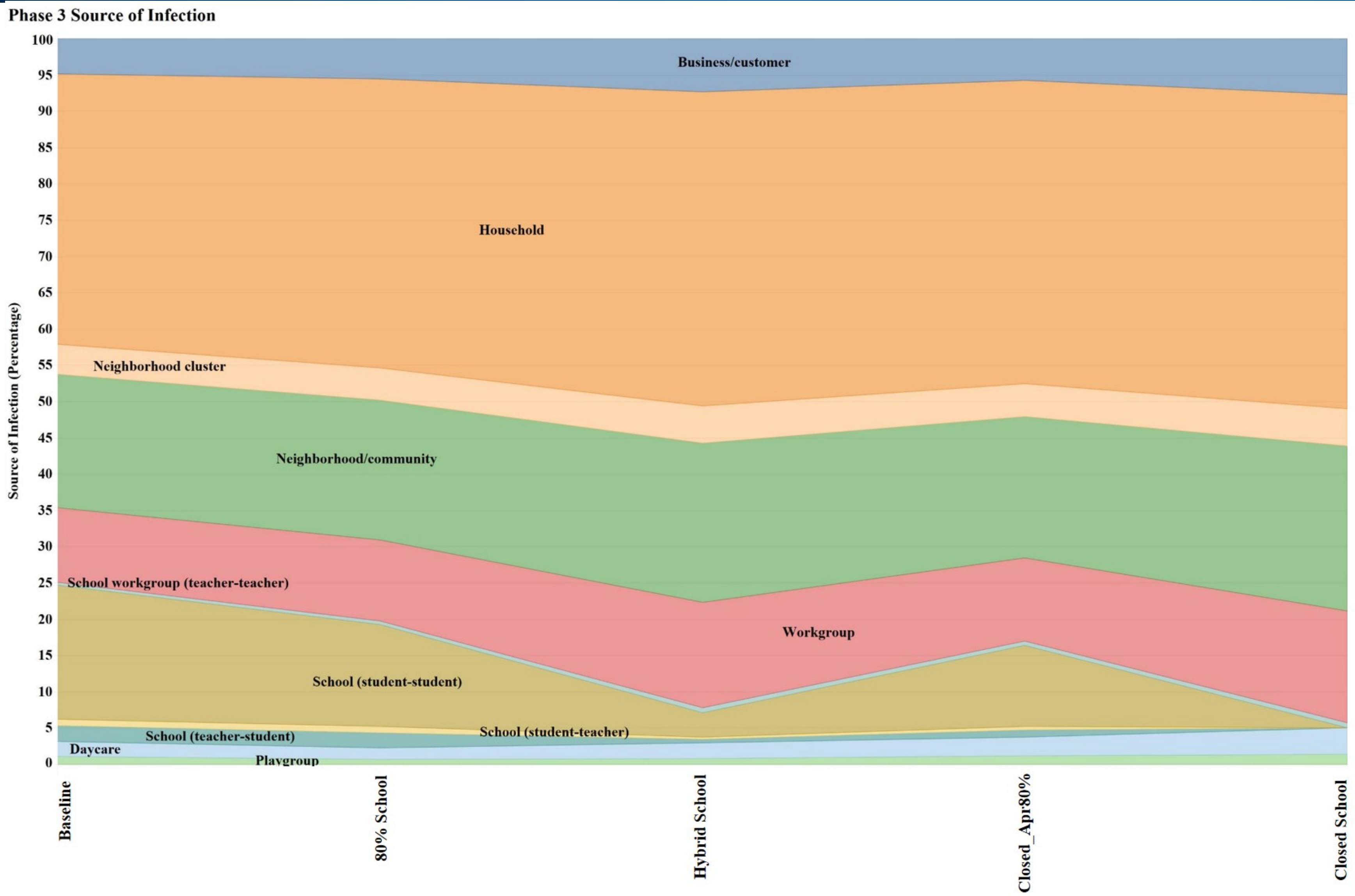
NM: Source of Infection for All Scenarios



So What?

- The majority of infections are generated at home and neighborhood/community
- Although the 80% school attendance scenarios generate about 20% of infections in school settings, they significantly increase the overall spread
- The hybrid learning scenarios lead to about 5% source of infection in school settings

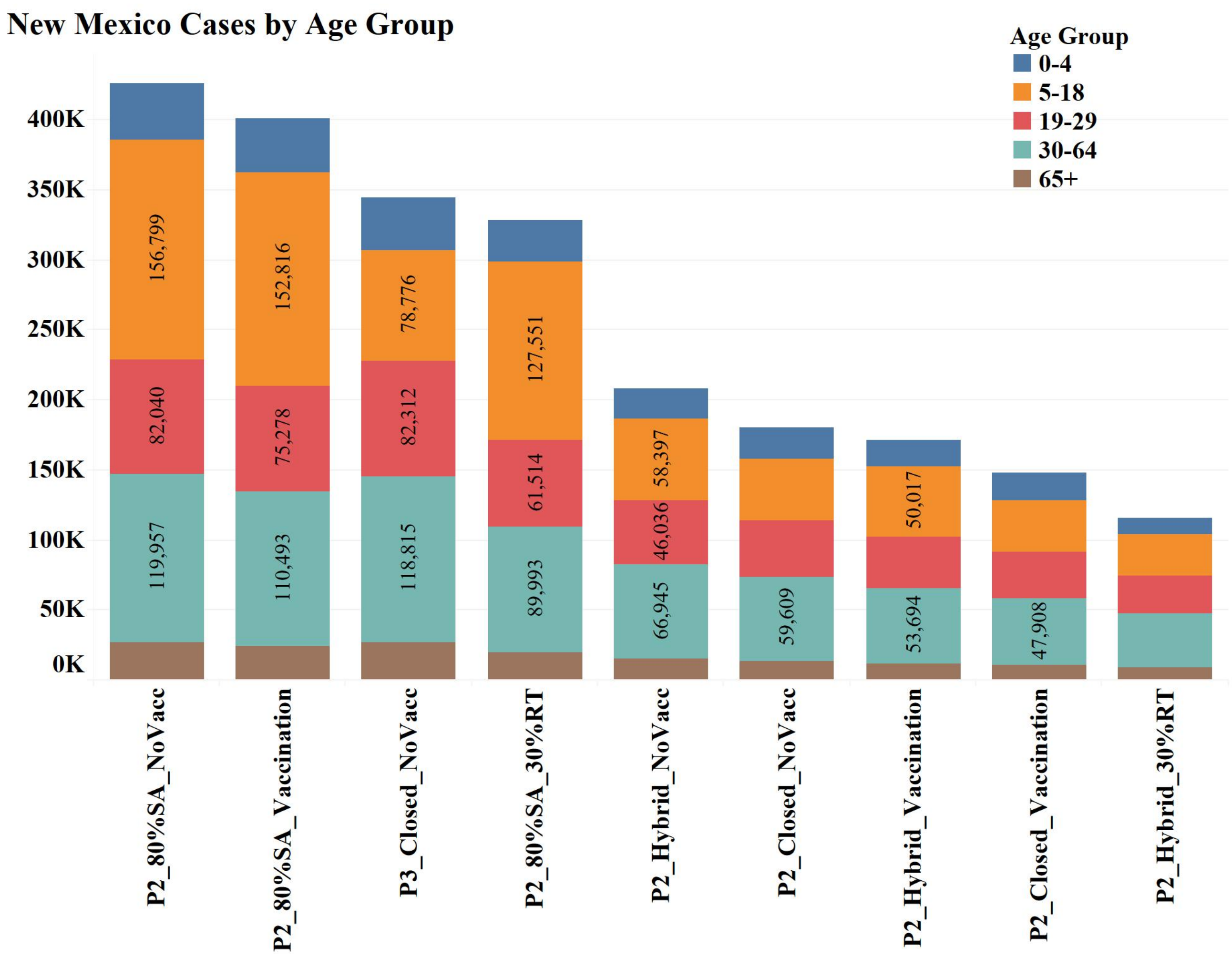
U.S.: Source of Infection (Phase 3)

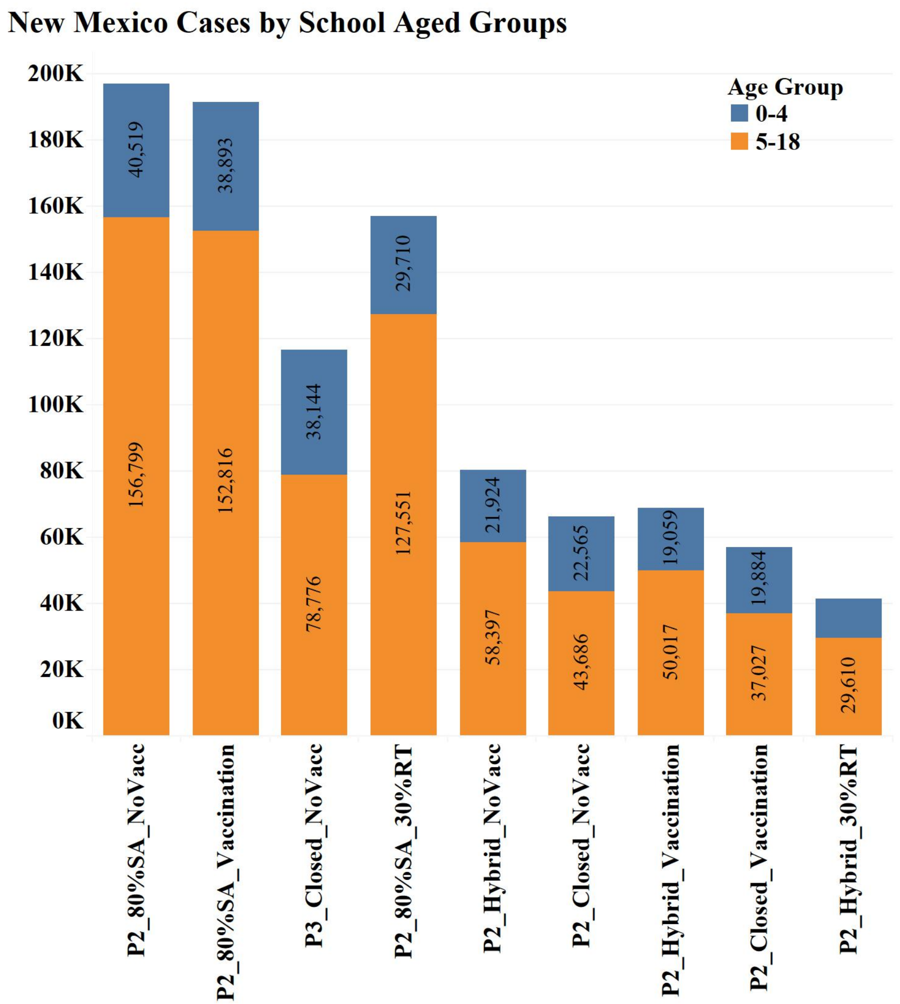


So what?

- The source of infection breakdowns for both Phase 2 and Phase 3 are similar
- The majority of cases are generated at home followed by neighborhood/ community/cluster
- Schools generate a significant number of cases for the 100%, 80%, and the April reopening scenarios

NM: Impacts by Age for All Scenarios

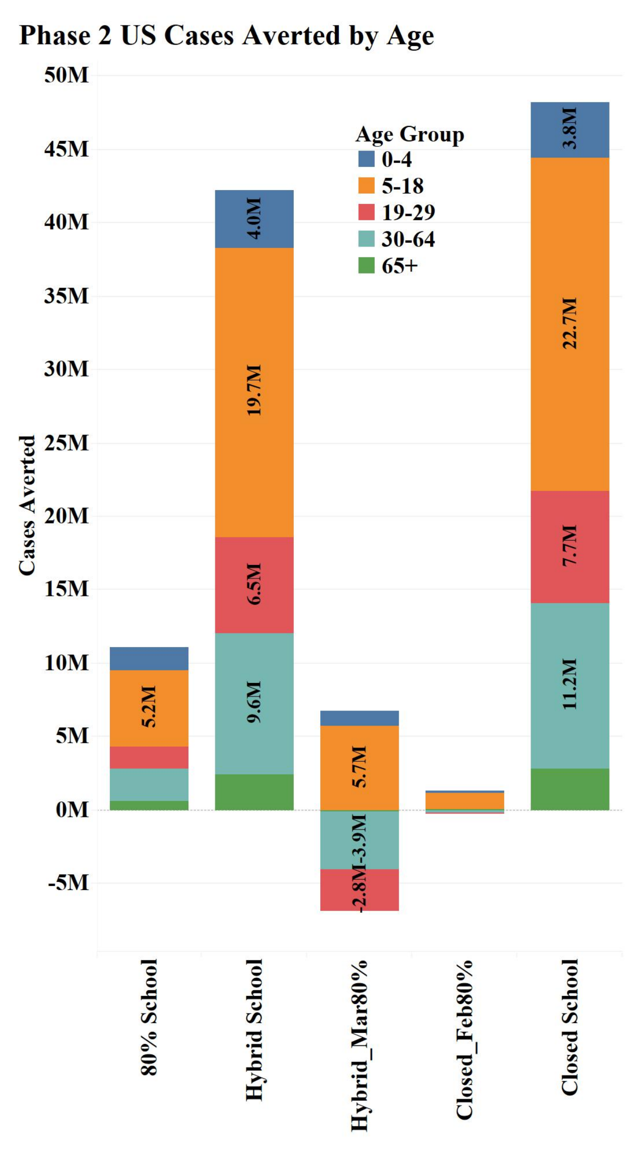


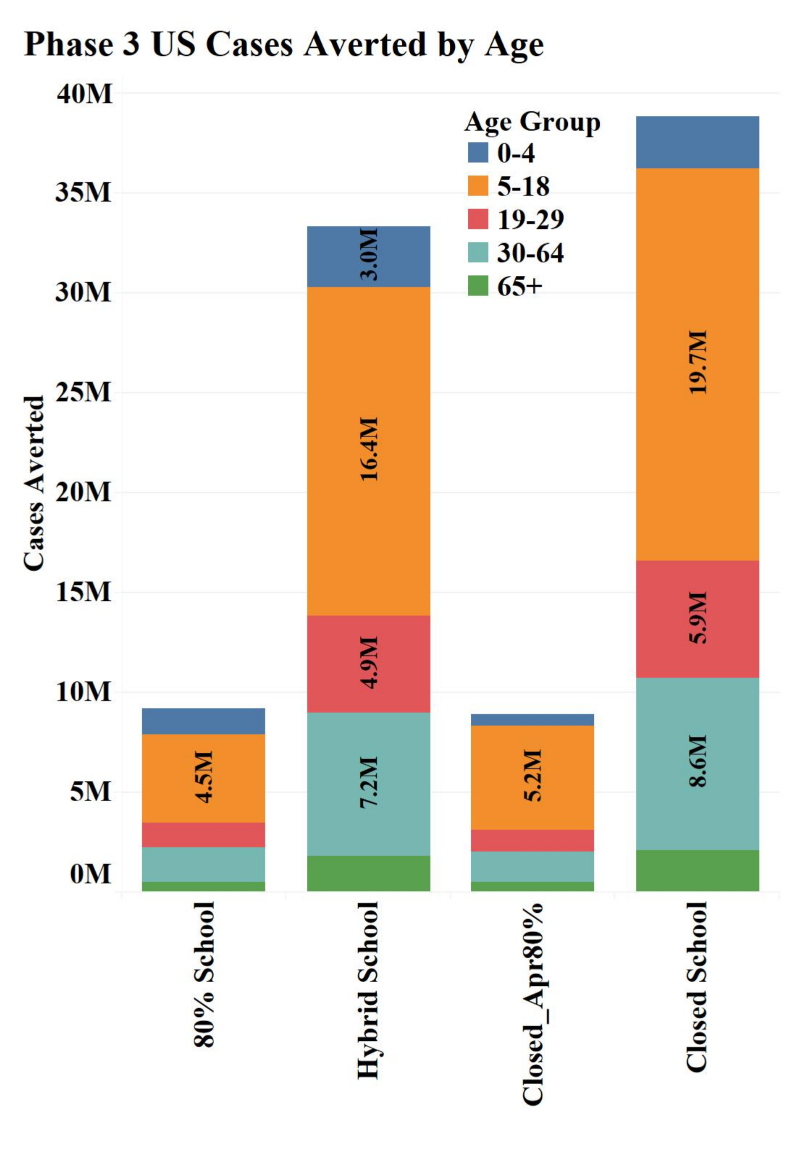


So What?

Staying in Phase 2 in combination with vaccine and either hybrid or virtual learning lead to better outcomes

U.S.: Impacts by Age for All Scenarios

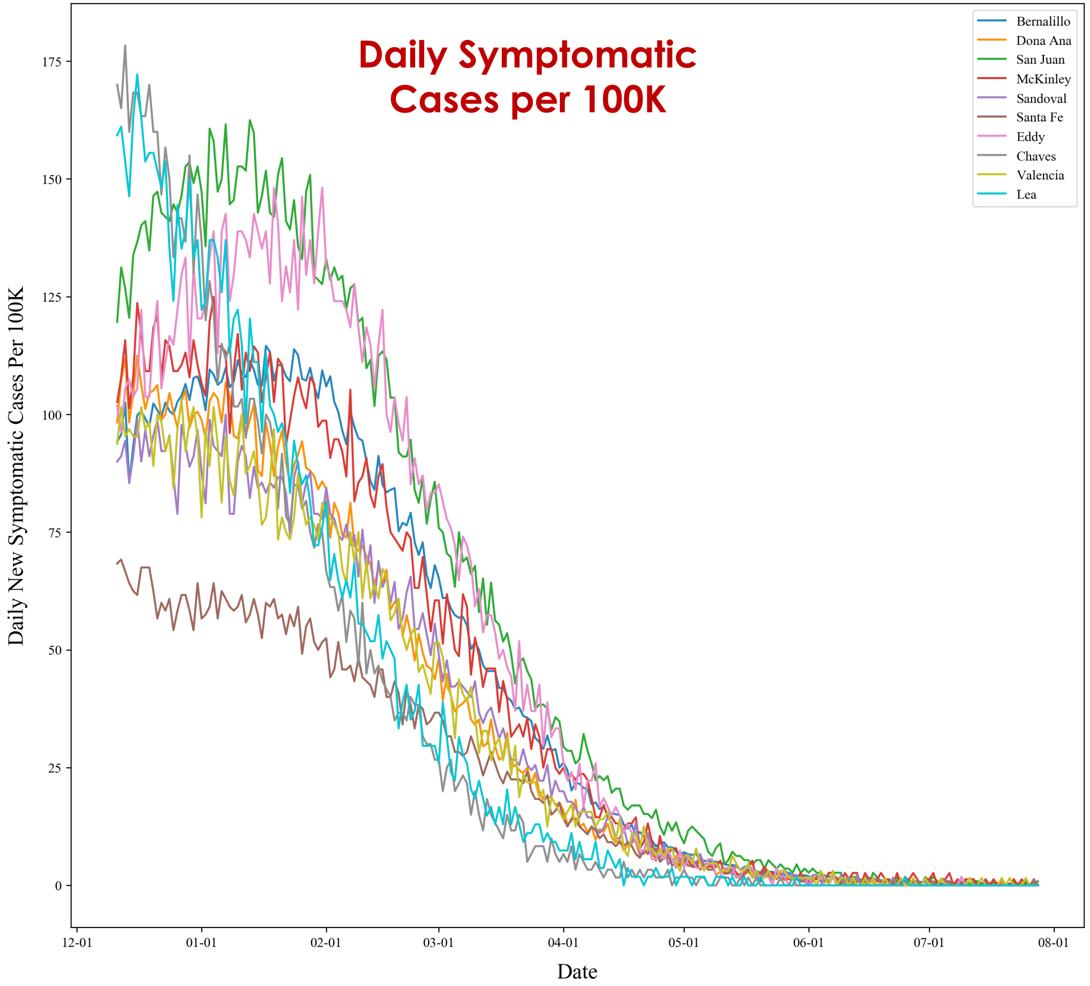


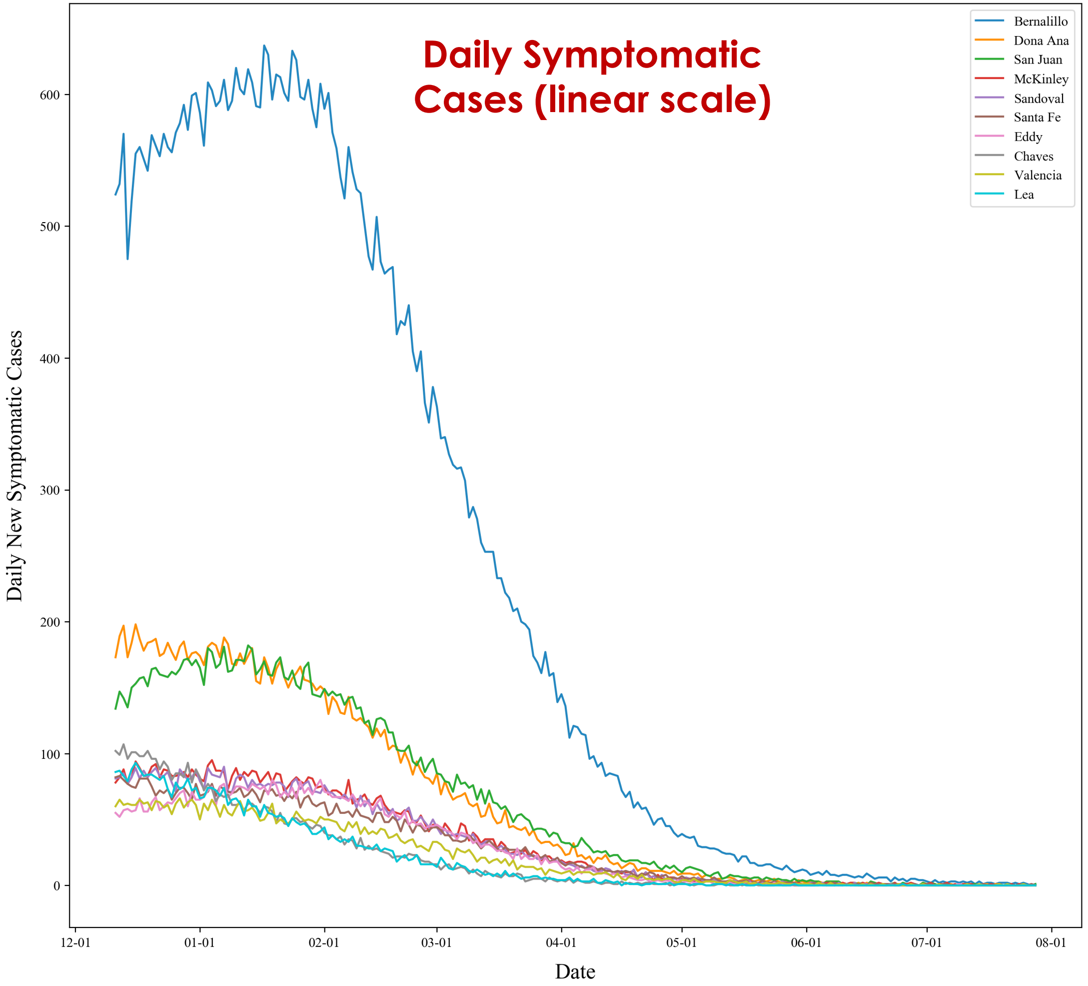


So what?

- Limited business activity (Phase 2) and hybrid school avert significant number of cases (~300K for NM)
- Limited business activity (Phase 2) in combination of virtual learning averts the most cases with over 325K cases averted
- Increased business activity (Phase 3) leads to fewer averted cases (240K hybrid and nearly 300K virtual)
- Reopening the schools and increasing business activity too early can have a negative impact by resulting in negative cases averted in two age groups (19-29 and 30-64)

NM: Phase 2 + Hybrid Learning + Vaccine

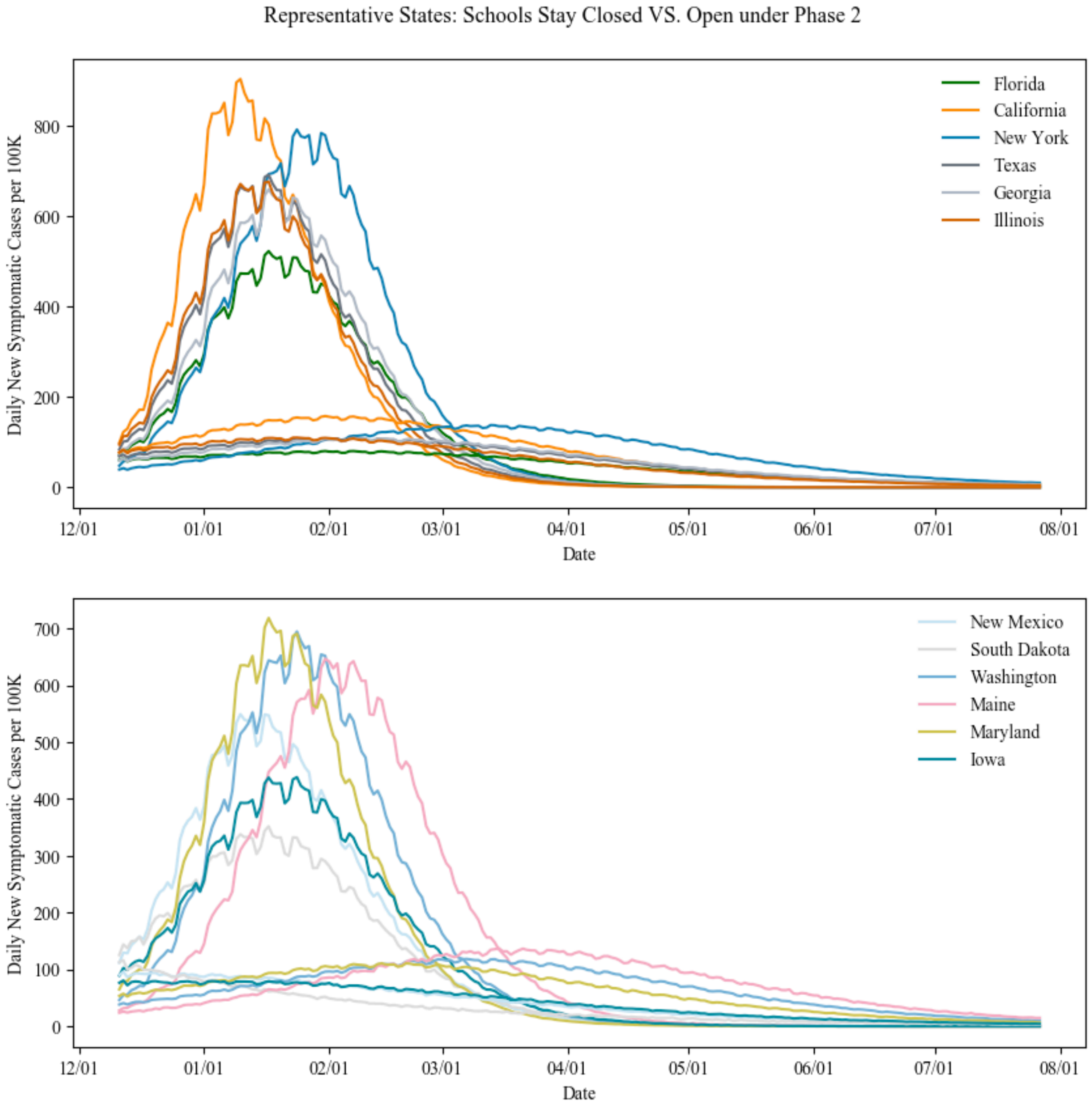


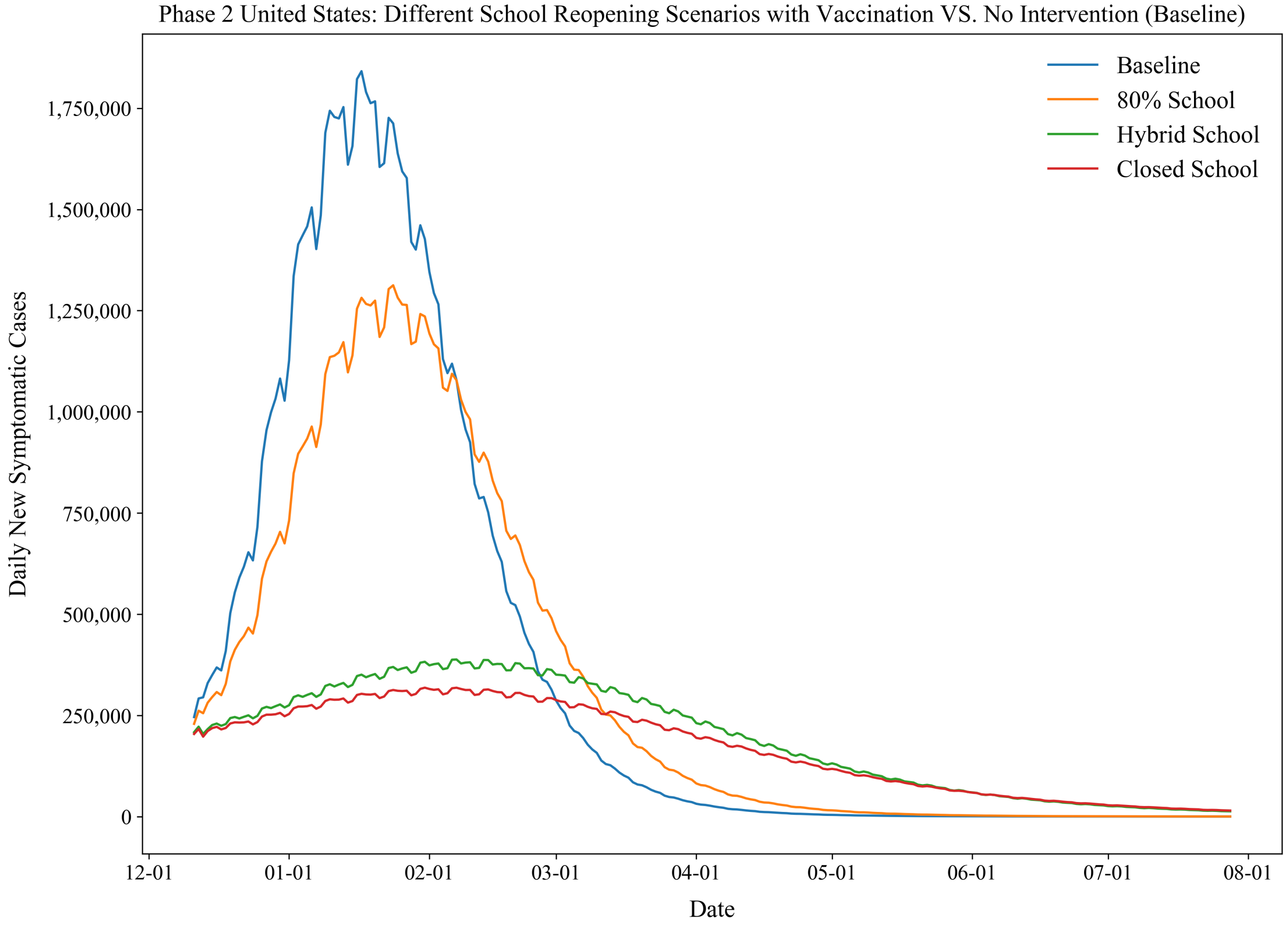


So What?

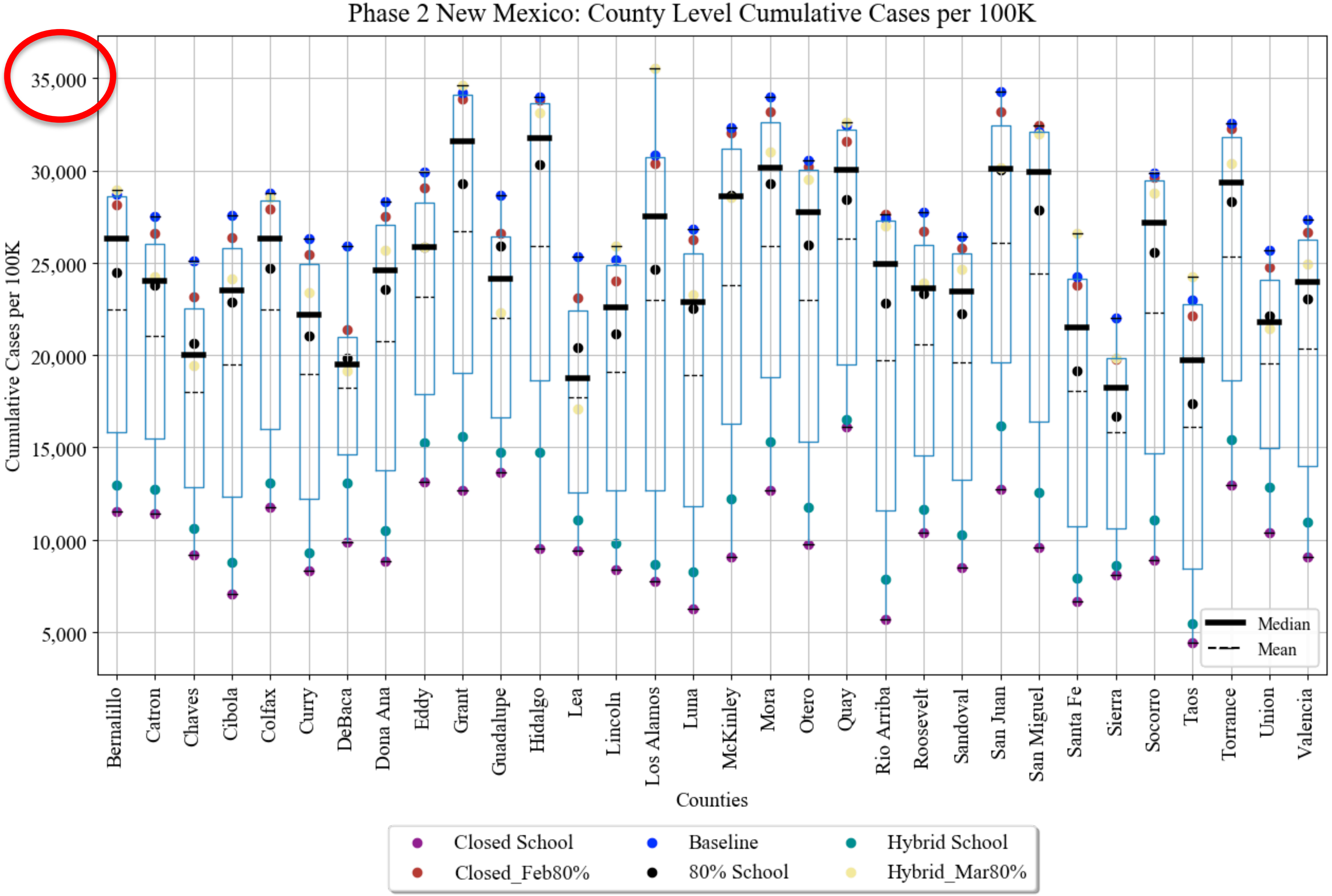
County-level differentiation for top 10 counties in NM

Phase 2: U.S. and 12 States Level Impacts for various scenarios





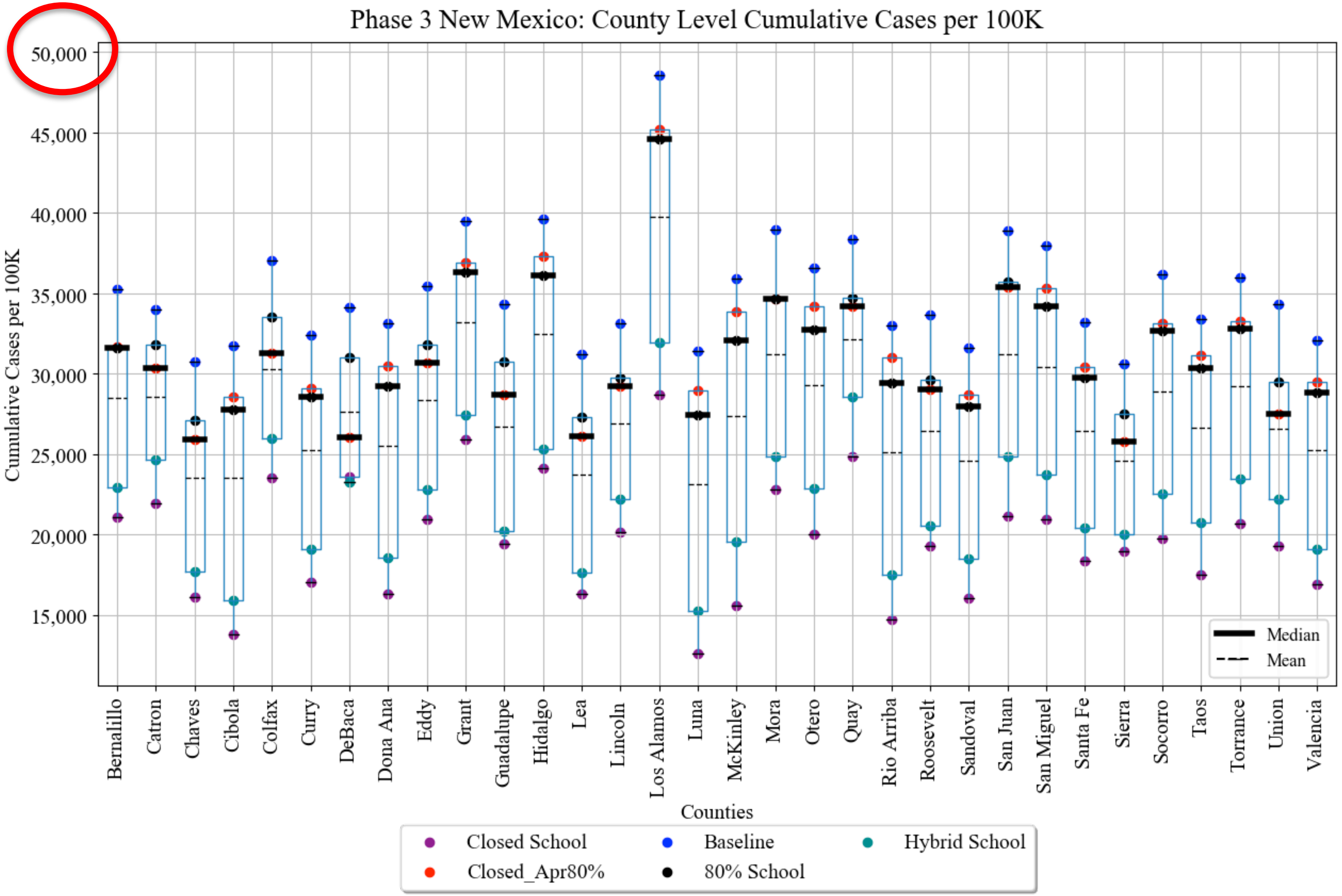
Phase 2: NM Impacts by County



So what?

- Fully reopening schools in areas with low incidence is likely to increase the risk of COVID-19 spread
- Flattening the curve through limited business activity and school activity (hybrid or virtual) is likely to result in better outcomes
- Spatial variability based on local demographics, initial conditions, and COVID-19 trends (% of population previously exposed)

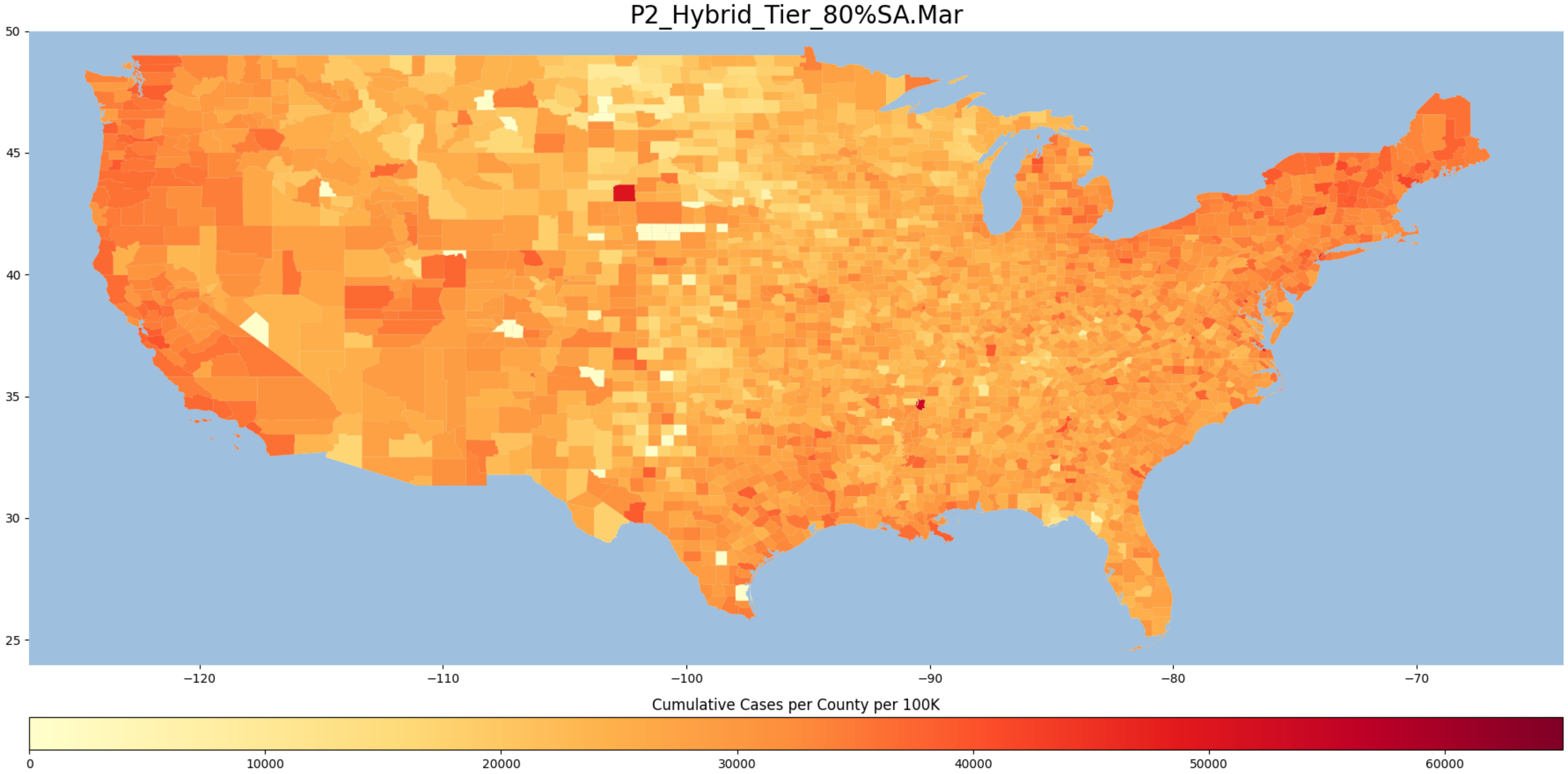
Phase 3: NM Impacts by County



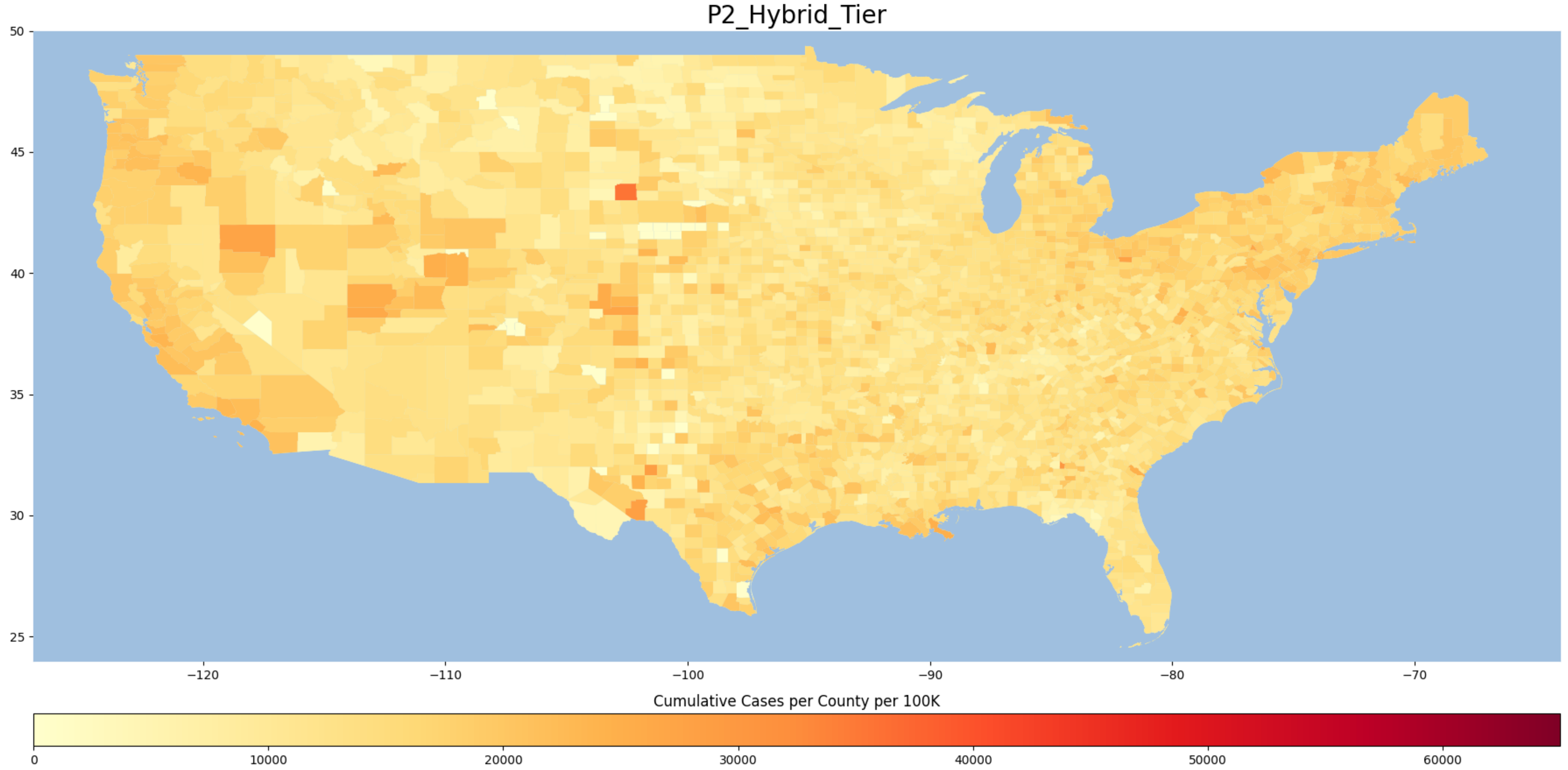
So what?

- Fully reopening schools and businesses in areas with low incidence is likely to increase the risk of COVID-19 spread
- Phase 3 (increased business activity) will lead to higher impacts across the region
- Spatial variability based on local demographics, initial conditions, and COVID-19 trends (% of population previously exposed)

U.S.: Cases per 100K for Phase 2/Hybrid/Vaccine Reopening Schools in March at 80%



U.S.: Cases per 100K for Hybrid/Phase 2/Vaccine



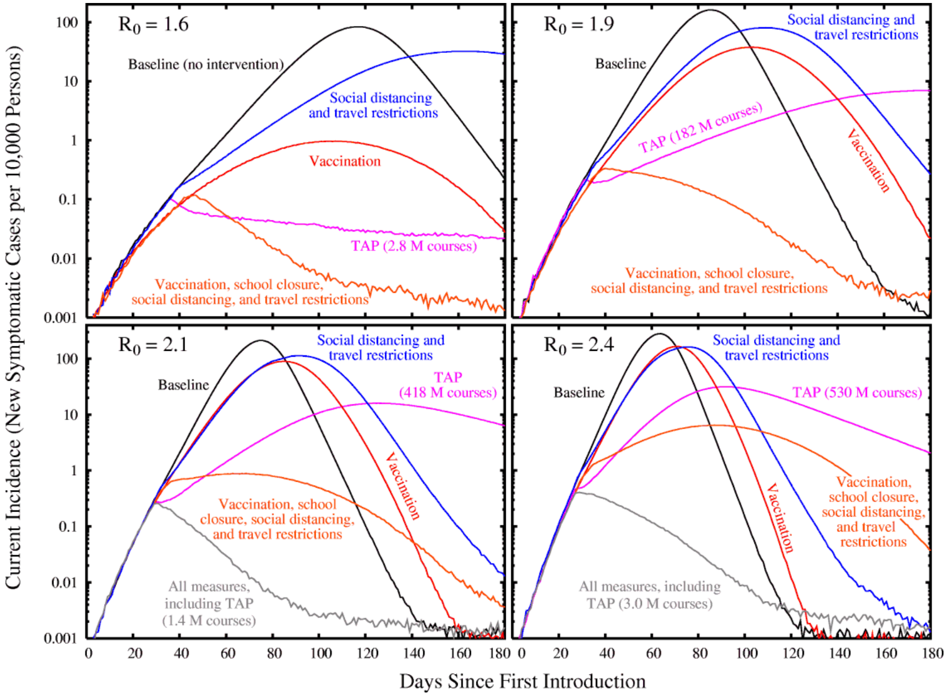
> Prior EpiCast Work

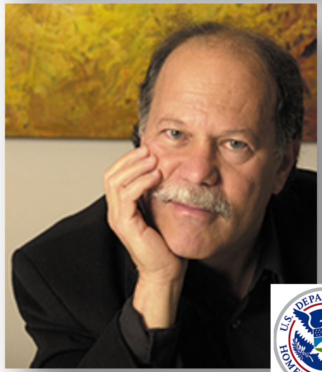
Initial Application of the National EpiCast Model with Tract-level Resolution was to Pandemic Influenza

Mitigation strategies for pandemic influenza in the United States

Timothy C. Germann*†, Kai Kadau*, Ira M. Longini, Jr.‡, and Catherine A. Macken*

*Los Alamos National Laboratory, Los Alamos, NM 87545; and ‡Program of Biostatistics and Biomathematics, Fred Hutchinson Cancer Research Center and Department of Biostatistics, School of Public Health and Community Medicine, University of Washington, Seattle, WA 98109

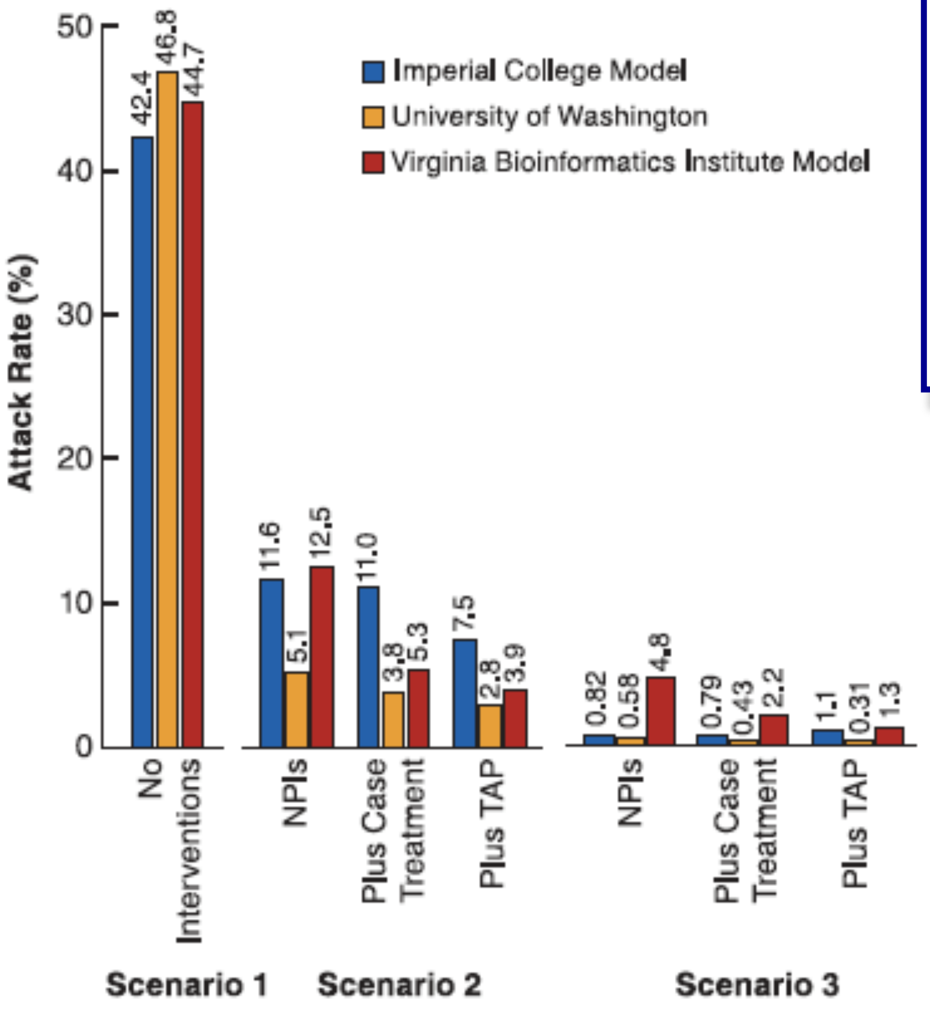




MIDAS
Models of Infectious Disease Agent Study

Homeland Security

Cross-model Comparison of Community-based Targeted Layered Containment Strategies



Modeling targeted layered containment of an influenza pandemic in the United States

M. Elizabeth Halloran*†‡, Neil M. Ferguson§, Stephen Eubank¶, Ira M. Longini, Jr.*†, Derek A. T. Cummings§, Bryan Lewis¶, Shufu Xu†, Christophe Fraser§, Anil Vullikanti¶, Timothy C. Germann‖, Diane Wagener**, Richard Beckman¶, Kai Kadau‖, Chris Barrett¶, Catherine A. Macken‖, Donald S. Burke††, and Philip Cooley**

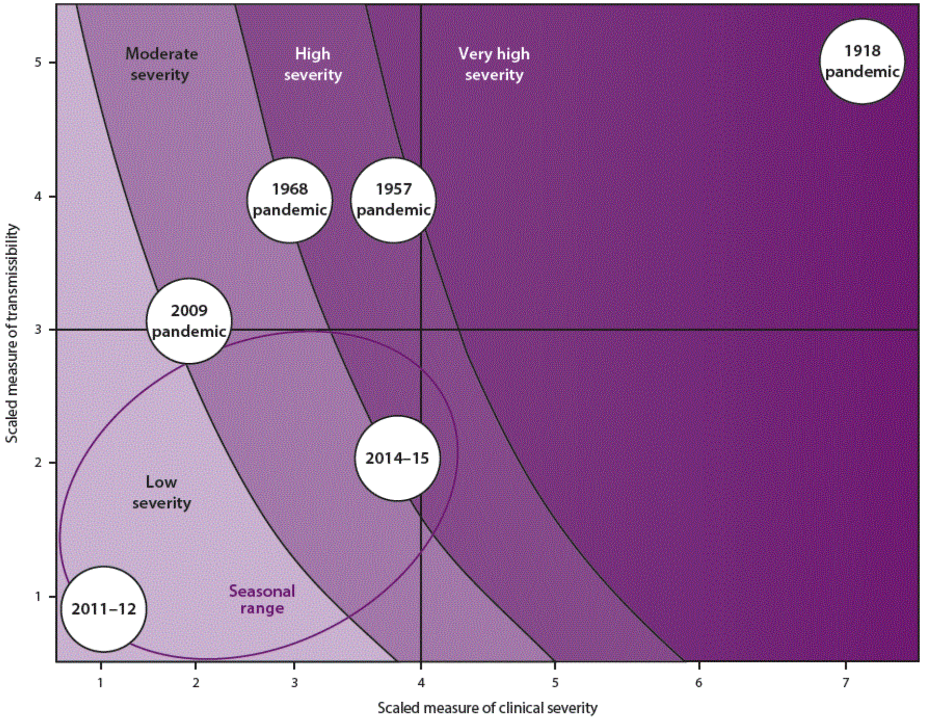
¶Virginia Bioinformatics Institute, Virginia Polytechnical Institute and State University, Blacksburg, VA 24061; ††Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA 15261; **Research Triangle Institute, Research Triangle Park, NC 27709; §Department of Infectious Disease Epidemiology, Imperial College, London W21PG, England; ‖Los Alamos National Laboratories, Los Alamos, NM 87545; *Department of Biostatistics, School of Public Health and Community Medicine, University of Washington, Seattle, WA 98195; and †Program in Biostatistics and Biomathematics, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA 98109

Edited by Barry R. Bloom, Harvard School of Public Health, Boston, MA, and approved January 15, 2008 (received for review July 23, 2007)

Table 3. Percentage of infections by place and scenario, R_0 = 1.9 (2.1) in the Chicago population

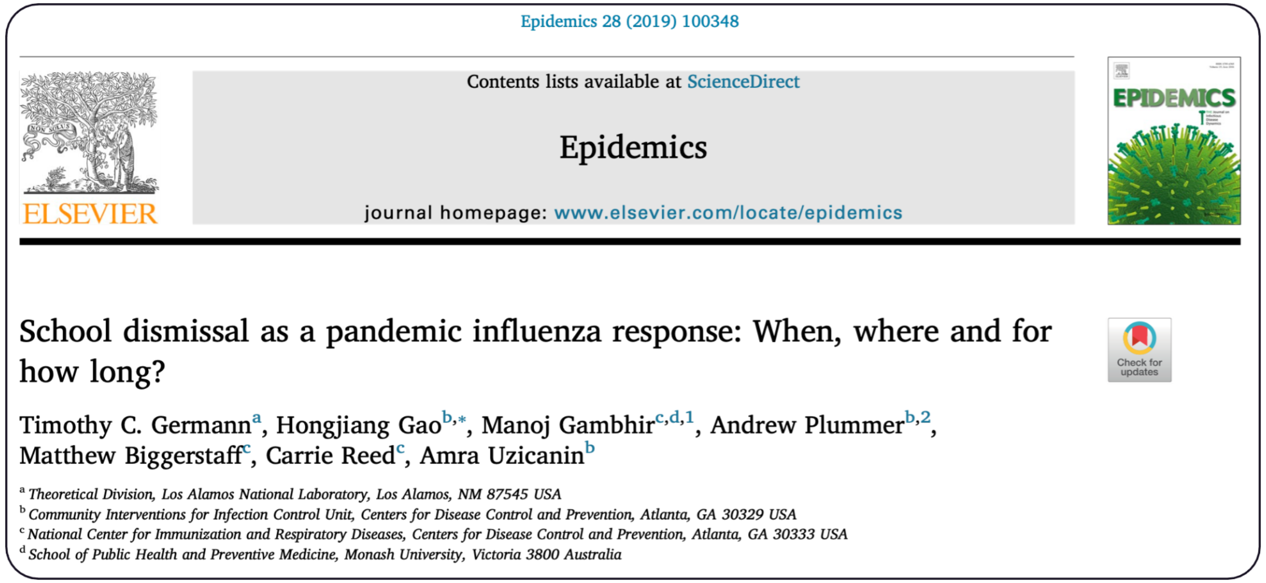
	Scenario 1. No intervention			Scenario 2			Scenario 3		
	Imperial	UW	VBI	Imperial	UW	VBI	Imperial	UW	VBI
Illness attack rates	42.4	46.8	44.7	7.3	2.8	3.9	1.1	0.31	1.3
Places									
Home	33.1	39.4	41.1	48.3	58	45.9	50.4	59	36.9
Work	21.8	14.5	28.6	12.9	10	27.8	13.5	10	18.7
School	16.0	18.8	23.3	11.7	11	9.6	9.0	11	2.7
Day care	–	1.1	–	–	0	–	–	0	–
Play group	–	0.8	–	–	0	–	–	0	–
College	–	–	3.3	–	–	12.3	–	–	40.0
Shopping	–	–	2.0	–	–	2.4	–	–	1.0
Neighborhood	–	17.7	–	–	15	–	–	15	–
Neighborhood clusters	–	7.7	–	–	5	–	–	4	–
Other/Community	29.0	0	1.7	26.6	0	2.0	23.8	0	0.8
Totals									
Primary Groups*	70.9	72.7	93.0	72.9	79	83.3	72.9	79	58.3
Community†	29.0	25.4	3.7	26.6	20	4.4	23.8	19	1.8

EpiCast Used to Assess School Dismissal Policies in the Context of the Pandemic Severity Framework



Adapted from C. Reed, M. Biggerstaff, L. Finelli, et al., ***Novel framework for assessing epidemiologic effects of influenza epidemics and pandemics***, Emerg Infect Dis **19**, 85–91 (2013)

CENTERS FOR DISEASE CONTROL AND PREVENTION



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School dismissal as a pandemic influenza response: When, where and for how long?

Timothy C. Germann[a], Hongjiang Gao[b,*], Manoj Gambhir[c,d,1], Andrew Plummer[b,2], Matthew Biggerstaff[c], Carrie Reed[c], Amra Uzicanin[b]

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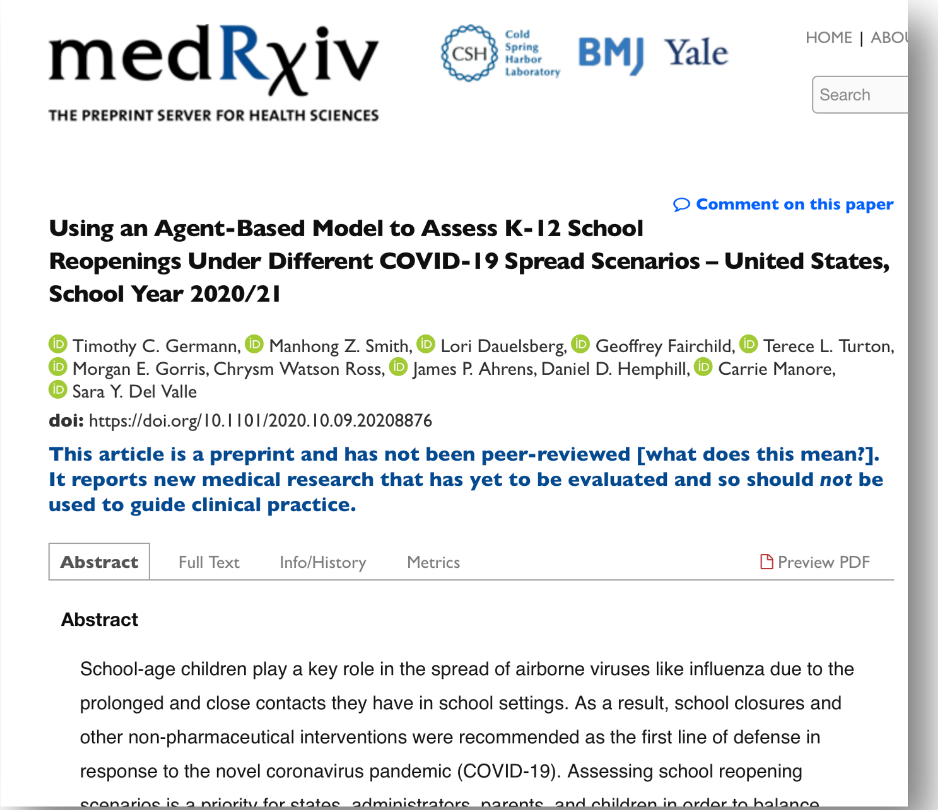
[d] School of Public Health and Preventive Medicine, Monash University, Victoria 3800 Australia

- In partnership with the **CDC Community Interventions for Infection Control Unit** (CI-ICU), we explored non-pharmaceutical interventions focused on school dismissal, specifically :
  - *Threshold trigger: **when** to close*
  - *Geographic scale: **where** to close*
  - *Duration: for **how long** to close*

Using Agent-Based Model to Assess K-12 School Reopening Under Different COVID-19 Spread Scenarios – United States, School Year 2020/21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Using an Agent-Based Model to Assess K-12 School Reopenings Under Different COVID-19 Spread Scenarios – United States, School Year 2020/21

Timothy C. Germann, Manhong Z. Smith, Lori Dauelsberg, Geoffrey Fairchild, Terece L. Turton, Morgan E. Gorris, Chrysm Watson Ross, James P. Ahrens, Daniel D. Hemphill, Carrie Manore, Sara Y. Del Valle

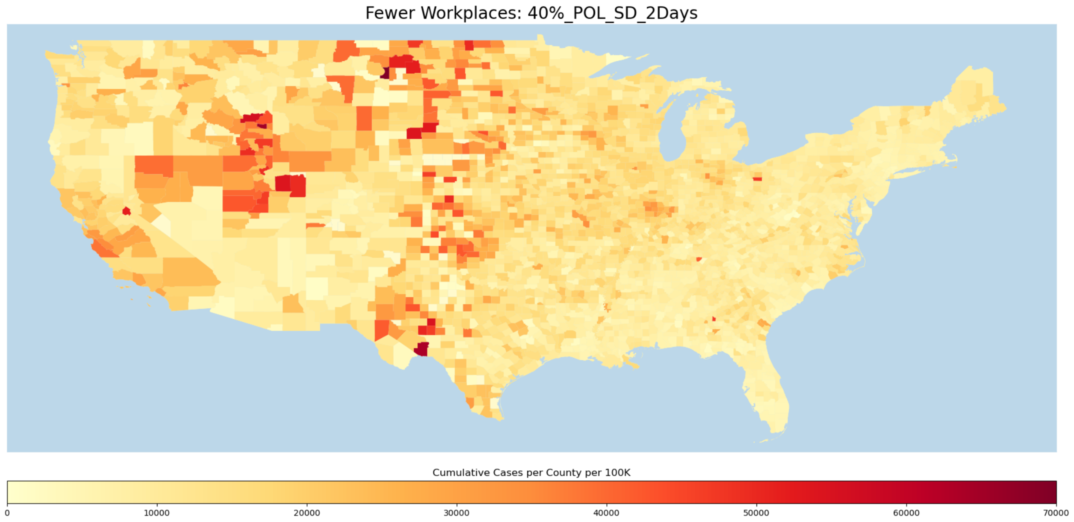
doi: https://doi.org/10.1101/2020.10.09.20208876

This article is a preprint and has not been peer-reviewed [what does this mean?]. It reports new medical research that has yet to be evaluated and so should *not* be used to guide clinical practice.

Abstract | Full Text | Info/History | Metrics | Preview PDF

Abstract

School-age children play a key role in the spread of airborne viruses like influenza due to the prolonged and close contacts they have in school settings. As a result, school closures and other non-pharmaceutical interventions were recommended as the first line of defense in response to the novel coronavirus pandemic (COVID-19). Assessing school reopening



CENTERS FOR DISEASE CONTROL AND PREVENTION

- In partnership with the **CDC Community Interventions for Infection Control Unit** (CI-ICU), we explored school reopenings under various assumptions:
  - *Impact of business activity*
  - *Reduced social distancing*
  - *Different school attendance schedules*

Epidemics 28 (2019) 100348

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School dismissal as a pandemic influenza response: When, where and for how long?

Timothy C. Germann[a], Hongjiang Gao[b,*], Manoj Gambhir[c,d,1], Andrew Plummer[b,2], Matthew Biggerstaff[c], Carrie Reed[c], Amra Uzicanin[b]

[a] *Theoretical Division, Los Alamos National Laboratory, Los Alamos, NM 87545 USA*
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ARTICLE INFO

Keywords:
Pandemic influenza
School dismissal
Stochastic individual-based model
EpiCast

ABSTRACT

We used individual-based computer simulation models at community, regional and national levels to evaluate the likely impact of coordinated pre-emptive school dismissal policies during an influenza pandemic. Such policies involve three key decisions: when, over what geographical scale, and how long to keep schools closed. Our evaluation includes uncertainty and sensitivity analyses, as well as model output uncertainties arising from variability in serial intervals and presumed modifications of social contacts during school dismissal periods. During the period before vaccines become widely available, school dismissals are particularly effective in delaying the epidemic peak, typically by 4–6 days for each additional week of dismissal. Assuming the surveillance is able to correctly and promptly diagnose at least 5–10% of symptomatic individuals within the jurisdiction, dismissals at the city or county level yield the greatest reduction in disease incidence for a given dismissal duration for all but the most severe pandemic scenarios considered here. Broader (multi-county) dismissals should be considered for the most severe and fast-spreading (1918-like) pandemics, in which multi-month closures may be necessary to delay the epidemic peak sufficiently to allow for vaccines to be implemented.

1. Introduction

Influenza pandemics occur when a novel influenza virus gains sustained human-to-human transmission and spreads globally, resulting in potentially high levels of morbidity and/or mortality. Following the emergence of a novel pandemic strain, several months are typically required to develop, produce, and distribute a well-matched pandemic vaccine (Gerdil, 2003; Centers for Disease Control and Prevention, 2010; President's Council of Advisors on Science and Technology, 2010). Moreover, the use of antiviral drugs for chemoprophylaxis may be limited due to concerns regarding drug resistance and limited supply during an evolving pandemic (Lipsitch et al., 2007; Centers for Disease Control and Prevention, 2011). As a result, non-pharmaceutical interventions (NPIs) are essential, potentially providing time for pandemic vaccines to be developed and distributed, decreasing the peak demand for healthcare services prior to pandemic vaccine roll-out, and reducing the overall morbidity and mortality caused by the novel virus. Among potential NPIs, school closure/dismissal has long been one of the first to be implemented during previous pandemics (Markel et al., 2007a; Cauchemez et al., 2009), given the major role that school-aged children play in the transmission of influenza in the household (Longini et al., 1982; Viboud et al., 2004) and community (Chao et al., 2010), likely due to intense social contacts among children in schools (Mossong et al., 2008).

In the absence of clear evidence for the effectiveness of school closures on large geographic scales, it has been very difficult for public officials to make policy recommendations and develop national guidance. Mathematical and computational disease spread models offer invaluable platforms for performing "what-if" studies to assess potential future pandemic scenarios and intervention strategies, complementing observational or field studies that are necessarily limited to historical events and decisions (Germann et al., 2006; Halloran et al., 2008). In particular, they enable us to model a variety of school dismissal strategies and assess their effectiveness in slowing the spread of a

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Available online 12 June 2019

Table 1
Summary of key EpiCast model parameters for this study (see Supporting Online Material and Germann et al (Germann et al., 2006) for further details).

Parameter	Options	Key attributes	
Pandemic scenario[a]	A(2009 like)	18% (32%, 15%, 7%), 1.3	Overall and age-specific (child, adult, elderly[b]) attack rates and R_0
	B1(1968 like)	22% (39%, 18%, 8%), 1.5	
	B2(1957 like)	28% (50%, 23%, 11%), 1.8	
	C(H5N1 like)	10% (18%, 8%, 4%), 1.2	
	D(1918 like)	30% (54%, 25%, 12%), 2.0	
Serial interval[c]	Short	1.98, 1.98, 1.61 days	Mean latent, incubation, and infectious period durations
	Long	1.2, 1.9, 4.1 days	
School dismissal trigger[d]	1%	100	Diagnosis ratio[c] (percentage of symptomatic individuals correctly identified) and corresponding number of symptomatic schoolchildren in a community required to trigger dismissal
	5%	20	
	10%	10	
	20%	5	
School dismissal duration	1, 2, 4, 8, and 12 weeks		and 16, 20, 24 weeks for scenario D
School dismissal geographic scale	Community		For regional model: Community or Regional
	County		
	Multi-county		
	State		
Child-related contact changes during dismissal	Worst-case	100% increase in child-related household contacts	
		30% reduction in child-related non-household contacts	
	Best-case	No change in child-related household contacts	
		50% reduction in child-related non-household contacts	

[a] Pandemic scenarios are based on a two-dimensional framework recently developed by (Reed et al. (2013)).
[b] Ages 0–18 years are considered children, 19–64 adult, and 65+ years elderly.
[c] The serial interval, or generation time, is the interval between successive cases in a chain of transmission.
[d] School dismissal is triggered when the first confirmed symptomatic school-age child is detected in a community. The diagnosis ratio is the percentage of symptomatic individuals that are positively identified; for instance, with a 5% diagnosis ratio, the first confirmed case may not be identified until 20 children are symptomatic.

hypothetical future influenza pandemic (Haber et al., 2007; Milne et al., 2008; Halder et al., 2010; Lee et al., 2010; Halder et al., 2011; Brown et al., 2011; Milne et al., 2013; Nishiura et al., 2014; Fung et al., 2015). However, previous pre-pandemic policy recommendations used a measure of pandemic severity that was based on disease severity measures, such as case fatality ratio and excess death rate (Centers for Disease Control and Prevention, 2007), while modeling studies primarily considered the effectiveness of school dismissal strategies for various disease transmissibility levels, usually represented by the basic reproduction number R_0 (Germann et al., 2006; Halloran et al., 2008; Harber et al., 2007; Milne et al., 2008; Halder et al., 2010; Lee et al., 2010; Halder et al., 2011; Brown et al., 2011; Milne et al., 2013; Nishiura et al., 2014; Fung et al., 2015). A recently developed two-dimensional pandemic severity assessment framework considers both transmissibility and clinical severity as two independent factors (Reed et al., 2013). This framework provides the basis for the development of national pre-pandemic NPI guidance, for which school closure is thought to be one of the most effective early mitigation measures. The purpose of the present study is to evaluate whether school dismissal should be recommended and, if so, when such dismissals should be initiated, how broadly (in geographic terms, e.g., community, county, or state-wide dismissals), and how long they should last. As described in the ***Methods***, we utilize simulations at three different scales to answer these questions in a computationally feasible manner. A single community model (˜2000 people) is used for sensitivity studies, and a regional model (˜8.6 million people in the Chicago metropolitan area) to address timing ("when" and "how long") and local vs. regional dismissal policies. The insights gleaned from these smaller-scale simulations are then used to design the final simulation suite, employing a model of the continental United States (˜300 million people).

2. Methods

2.1. Simulation platform

In the present work, we extend and apply the stochastic, individual-based EpiCast ("Epidemiological Forecasting") model (Germann et al., 2006; Halloran et al., 2008) to evaluate a range of school dismissal policy options for five potential influenza pandemic strains having characteristics based upon both historical (1918, 1957, 1968, and 2009) and potential H5N1-like pandemics, spanning the four quadrants (with independent severity and transmissibility axes) of the pandemic severity assessment framework (Reed et al., 2013). Full details about EpiCast are provided in the SI.

2.2. Model parameters and assumptions

For each of these five pandemic scenarios and three geographical scales, four other parameters are varied (see Table 1) in order to span their likely ranges and ascertain their impact on mitigation. First, we consider two alternative disease natural histories ("Short" and "Long"), with serial intervals (average time between successive cases) of ˜2.8 and 4 days, respectively. These two choices have been used in several previous modeling studies (Halloran et al., 2008), and almost exactly span the 95% confidence interval of 2.9–4.3 days observed in a household study during the 2007 interpandemic influenza season in Hong Kong (Cowling et al., 2009)

Second, we considered different triggers for school dismissal, all involving the diagnosis of some threshold number of symptomatic school children within a community. Once that threshold is reached, all schools within that community are closed, and possibly those in surrounding communities, depending upon the specific policy. Since it will be impossible to quickly identify and accurately diagnose all symptomatic children, the surveillance sensitivity is an important factor. In the present study, no other actions (e.g., therapeutic antivirals, isolation, or quarantine) other than self-isolation (staying home when sick, as specified in SI section 1 F) are taken following diagnosis. Consequently, the diagnosis ratio (the percentage of newly symptomatic individuals correctly and promptly identified following illness onset) and the trigger threshold (the number of diagnosed school children required to activate a dismissal) can be coupled to provide a single independent parameter for the trigger, the number of symptomatic (but not necessarily diagnosed) school children. For example, if the diagnosis of a single child is sufficient to trigger intervention, then diagnosis ratios of 1%, 5%, 10%, and 20% require 100, 20, 10, and five symptomatic school children, respectively, in a community before the first symptomatic child is diagnosed, triggering the intervention.

Third, the geographic scale of school dismissal can range from the individual community (which may be considered as a very small ˜2000-person school district), to single county, multi-county, or even potentially state- or nation-wide closures in the most severe situation, as in the 1918-like scenario D. With the regional model, we consider school dismissal at either the individual community or region-wide levels, and at the national scale consider four scales of dismissal: community, county, adjoining county region, or (for the 1918-like scenario D only) state-wide dismissals.

Finally, in the face of a limited amount of survey and field study data on social contact behaviors in and out of school from the United States (Mossong et al., 2008; Gog et al., 2014; Earn et al., 2012; Copeland et al., 2013; Chowell et al., 2011; Heymann et al., 2004; Markel et al., 2007; Eames et al., 2012), we utilize a range of assumed social contact pattern changes during school dismissal that is consistent with the available studies and span those used in previous modeling work (Germann et al., 2006; Halloran et al., 2008; Haber et al., 2007; Milne et al., 2008; Halder et al., 2010; Lee et al., 2010; Halder et al., 2011; Brown et al., 2011; Milne et al., 2013; Nishiura et al., 2014; Fung et al., 2015). Since these contact rates contribute to the infection probability for each susceptible person, they have a strong influence on overall disease transmission, and unrealistic assumptions (e.g., "no contacts between children during school dismissal") can lead to overly optimistic expectations for the benefits of school dismissal. To provide likely bounds on the effectiveness of school dismissal policies for each combination of school dismissal policy and pandemic scenario, we consider two assumptions, representing either a "worst-case" (with a greater amount of contact during closure, in which household contacts involving children are doubled, and child-related contacts outside the home are reduced by only 30%) and a "best-case" (with no change in household contacts and a 50% reduction in outside contacts) scenario. In both cases, all schools, preschools, daycares, and playgroups within the affected community (or communities) are closed during dismissal, so no transmission occurs within these mixing groups. Social contact surveys (Eames et al., 2012) and mathematical model-based analysis of virological data (Earn et al., 2012) during the 2009 summer and fall holiday breaks suggest that there is a reduction of at least 40–50% in contact and transmission among school-age children during such regularly scheduled dismissals; pre-emptive coordinated school dismissals undertaken as a countermeasure during an evolving pandemic would likely lead to additional precautions, reducing contacts even further.

We also assume that a well-matched vaccine will be available 6 months after the first U.S. index case. The assumed vaccine efficacy for susceptibility VEs = 0.70 (VEs = 0.50 for age 65+) represents the reduced susceptibility to infection and influenza illness of vaccinated individuals, while the vaccine efficacy for infectiousness VEi = 0.80 (for all age groups) represents the reduced infectiousness to others (Longini et al., 2000). Full details about vaccine assumption are described in the SI. To separate the effects of school dismissal alone from that coupled with a vaccination campaign, we will measure cumulative attack rates both before (on day 180) and after (on day 240) vaccine introduction.

2.3. Sensitivity analysis

A model of a single community of 2000 persons is used to identify the key model parameters and quantify their impact on the mitigation of disease spread (Blower and Dowlatabadi, 1994). We consider six contact settings: households, household clusters, neighborhoods, communities, schools, and workplaces. Latin hypercube sampling is used to sample the contact probability in each setting, then partial rank correlation coefficients are calculated as the outcome measure for sensitivity analysis. Full details are presented in the SI.

2.4. Model parameter calibration

The model of a small community was also used to develop an initial set of model parameters for each of the five pandemic scenarios under consideration (Table 1). The specified age-specific attack-rate patterns, basic reproduction number R_0, and case fatality ratios were fit by adjusting the baseline EpiCast model contact rates (Germann et al., 2006) to give age-specific and overall attack rates within 1% of the specified values. For instance, in order to increase the childhood attack rate, the corresponding school contact rate is increased. Similarly, to increase the working-age adult attack rate, the workplace contact rate is raised.

2.5. Scoping studies

The regional (Chicago-area) model was used for an earlier study involving EpiCast and two other individual-based, stochastic simulation models (Halloran et al., 2008). Here, we use it for scoping studies to evaluate the impact of the trigger and duration of school dismissal, which will then be used to down-select to a smaller number of scenarios to be evaluated using the more computationally expensive national-scale model. The baseline parameters for each pandemic scenario are adjusted slightly from their single-community values (reflecting the more dispersed and heterogeneous population structure of the larger-scale model), giving the model parameters listed in Table S1 and baseline epidemic curves shown in Fig. S2. School dismissal options are then systematically studied by considering all possible combinations of the model parameters listed in Table 1. With regard to the geographic scale, this model considers either community-by-community or simultaneous region-wide school dismissals. Furthermore, for the most severe and transmissible 1918-like scenario D, longer durations of closure (e.g., 16–24 weeks) are also explored.

2.6. National-scale simulation studies

For simulations of pandemic spread across the continental United States, the manner of introduction of a pandemic influenza strain must be considered. In particular, a human-transmissible strain may emerge either domestically or overseas, in both cases most likely in a rural area. As discussed in the SI, the subsequent epidemic will slowly spread through the more dispersed rural population before reaching a dense urban population where it can thrive, and it is during this early, rural, spread, whether in the U.S. or overseas, that early characterization and vaccine development can begin. One plausible domestic emergence scenario is modeled by the introduction of 10 infected individuals into Sussex County, Delaware, a large poultry-farming region on the Delaware-Maryland-Virginia (DelMarVa) peninsula. Previous studies (Germann et al., 2006) have found that introduction via air travel into major metropolitan areas, or point source introductions into large cities (either New York or Los Angeles), result in nearly identical national-level incidence rates, with only a difference in the details of the spatiotemporal spread. Consequently, we assume an introduction via arriving international air passengers (2 per 10,000) for this overseas scenario, a rate comparable with that used for the regional model.

Given the greatly increased computational cost of the national-scale model, the comprehensive set of regional model results is used to identify the most useful set of larger-scale simulations. As the two scenarios with the highest clinical severity and the least and most transmissible spread, pandemic scenarios C and D are both included in the national-scale study. School dismissal is unlikely to be invoked for the low-transmissibility, low-severity scenario A, so it is not considered further. While there are subtle differences in results for scenarios B1 and B2, we focus on B2 due to its higher severity and transmissibility than B1. We consider three geographic scales of school dismissal for each of these scenarios: community, county, multi-county region (including the affected county and all immediately adjacent counties), and additionally a coordinated (simultaneous) state-wide dismissal for the

Table 2
Cumulative attack rates (AR) with the reduction from the baseline scenario in parentheses (δ) using the regional model, with the shorter (mean ˜2.8 day) serial interval and best-case contact pattern change (a 50% reduction in non-household contacts) during school dismissal. Analogous tables for the longer serial interval and/or worst-case contact patterns are provided in the SI.

Pandemic scenario	Baseline Clinical Attack Rate[a]	Trigger	Community School Dismissal[c]					Regional School Dismissal[c]				
		Diag. ratio[b]	Duration					Duration				
			1 wk AR(δ)	2 wks AR(δ)	4 wks AR(δ)	8 wks AR(δ)	12 wks AR(δ)	1 wk AR(δ)	2 wks AR(δ)	4 wks AR(δ)	8 wks AR(δ)	12 wks AR(δ)
A (2009-like)	18.4%	1%	18.4 (0.0)	18.4 (0.0)	18.4 (0.0)	18.4 (0.0)	18.4 (0.0)	18.4 (0.0)	18.4 (0.0)	18.4 (0.0)	18.4 (0.0)	18.4 (0.0)
		5%	17.1 (1.3)	16.6 (1.8)	16.4 (2.1)	16.2 (2.2)	16.1 (2.3)	17.9 (0.5)	17.3 (1.1)	14.9 (3.5)	8.2 (10.2)	3.0 (15.4)
		10%	14.6 (3.8)	12.8 (5.6)	11.8 (6.6)	10.9 (7.5)	10.5 (7.9)	18.1 (0.4)	17.4 (1.0)	15.0 (3.4)	9.7 (8.7)	4.5 (13.9)
		20%	12.5 (5.9)	8.4 (10.0)	6.0 (12.4)	5.0 (13.4)	4.5 (13.9)	17.9 (0.5)	17.1 (1.3)	15.9 (2.5)	10.7 (7.7)	5.0 (13.4)
B1 (1968-like)	22.6%	1%	22.6 (0.0)	22.6 (0.0)	22.6 (0.0)	22.6 (0.0)	22.6 (0.0)	22.6 (0.0)	22.6 (0.0)	22.6 (0.0)	22.6 (0.0)	22.6 (0.0)
		5%	21.1 (1.5)	20.6 (2.0)	20.2 (2.4)	19.7 (2.9)	19.5 (3.0)	22.5 (0.1)	22.3 (0.3)	21.6 (1.0)	15.6 (7.0)	7.9 (14.7)
		10%	19.4 (3.2)	17.9 (4.6)	16.3 (6.3)	14.2 (8.4)	13.3 (9.3)	22.5 (0.1)	22.4 (0.2)	21.7 (0.9)	17.2 (5.3)	9.6 (13.0)
		20%	18.9 (3.7)	16.0 (6.6)	12.6 (10.0)	9.2 (13.4)	7.5 (15.0)	22.5 (0.1)	22.4 (0.2)	22.0 (0.6)	18.3 (4.3)	10.5 (12.0)
B2 (1957-like)	28.3%	1%	28.3 (0.0)	28.3 (0.0)	28.3 (0.0)	28.3 (0.0)	28.3 (0.0)	28.3 (0.0)	28.3 (0.0)	28.3 (0.0)	28.3 (0.0)	28.3 (0.0)
		5%	25.6 (2.7)	24.5 (3.8)	23.3 (5.0)	22.0 (6.4)	21.4 (6.9)	28.3 (0.1)	28.3 (0.0)	28.2 (0.1)	27.0 (1.3)	19.7 (8.7)
		10%	25.2 (3.1)	23.8 (4.5)	21.5 (6.9)	16.7 (11.6)	14.0 (14.4)	28.2 (0.1)	28.3 (0.0)	28.2 (0.1)	27.2 (1.1)	20.7 (7.6)
		20%	26.2 (2.1)	24.8 (3.5)	21.5 (6.8)	14.6 (13.7)	9.4 (18.9)	28.3 (0.0)	28.3 (0.1)	28.2 (0.1)	27.5 (0.8)	22.4 (5.9)
C (H5N1-like)	12.1%	1%	12.1 (0.0)	12.1 (0.0)	12.1 (0.0)	12.1 (0.0)	12.1 (0.0)	12.1 (0.0)	12.1 (0.0)	12.1 (0.0)	12.1 (0.0)	12.1 (0.0)
		5%	11.5 (0.6)	11.1 (1.0)	11.0 (1.1)	11.1 (1.0)	11.1 (1.0)	11.0 (1.1)	9.5 (2.6)	6.2 (5.9)	2.8 (9.3)	0.9 (11.2)
		10%	9.1 (3.0)	7.7 (4.4)	7.0 (5.1)	6.9 (5.2)	6.9 (5.2)	11.2 (0.9)	10.0 (2.1)	7.2 (4.9)	3.8 (8.3)	1.4 (10.7)
		20%	6.4 (5.7)	3.7 (8.4)	3.0 (9.1)	2.7 (9.4)	2.4 (9.7)	11.5 (0.6)	9.9 (2.2)	8.2 (3.9)	4.4 (7.7)	1.8 (10.3)
D (1918-like)	30.1%	1%	30.1 (0.0)	30.1 (0.0)	30.1 (0.0)	30.1 (0.0)	30.1 (0.0)	29.7 (0.4)	29.5 (0.6)	29.1 (1.0)	27.3 (2.8)	24.7 (5.4)
		5%	26.8 (3.3)	25.5 (4.6)	24.0 (6.1)	21.5 (8.6)	20.6 (9.5)	30.1 (0.0)	30.1 (0.0)	30.1 (0.0)	30.0 (0.1)	27.0 (3.1)
		10%	27.3 (2.8)	26.3 (3.8)	25.0 (5.1)	19.3 (10.8)	14.1 (16.0)	30.1 (0.0)	30.1 (0.0)	30.1 (0.0)	30.0 (0.1)	27.8 (2.3)
		20%	28.5 (1.6)	27.9 (2.2)	26.9 (3.2)	21.5 (8.6)	12.4 (17.7)	30.1 (0.0)	30.1 (0.0)	30.1 (0.0)	30.0 (0.1)	28.4 (1.7)

[a] Cumulative clinical attack rates (i.e., the percentage of the total population who develop clinical symptoms within 240 days of the index case, i.e. including 60 days after the vaccination campaign has started) are given for the baseline (no dismissal) scenario and various school dismissal policy options.

[b] School dismissal is triggered when the first confirmed symptomatic school-age child is detected in a community. The diagnosis ratio is the percentage of symptomatic individuals that are positively identified; for instance, with a 5% diagnosis ratio, the first confirmed case may not be identified until 20 children are symptomatic.

[c] Upon triggering a dismissal, either only the affected community's schools are closed (community dismissal) or a simultaneous dismissal of all Chicago-area schools (regional dismissal).

worst-case scenario D.

3. Results

3.1. Single community model

By attributing each new infection to a single source based on relative contributions of contacts to the overall transmission probability, we find that household transmission dominates (~40%), followed by the age-appropriate daytime mixing group (school or work) (~30%) and non-specific contact settings (also ~30%), both for the original contact parameters and for the modified contact parameters calibrated for the five pandemic scenarios (Fig. S3 in the Supplementary information (SI)). This is consistent with the pattern used in other modeling work, with perhaps a slightly increased household transmission. In accord with this finding, sensitivity analyses performed on the single-community model confirm that the assumed household, school, and workplace contacts (in that order) have the greatest impact on the resulting cumulative attack rate, with non-specific community transmission (which contributes to roughly a quarter of all cases) following closely behind. The relationship between these contact matrix elements and the epidemic timing is even more interesting. The partial rank correlation coefficient (PRCC) shown in Fig. S4, which measures the sensitivity of output variables to inputs, indicates that school transmission has, by far, the largest impact on the number of days from initial outbreak to peak incidence (a PRCC of −0.55), followed by household transmission (−0.27) (The negative values simply indicate that for *increasing* contact rates, the time to peak incidence *decreases*.). Interestingly, the workplace contact rate PRCC (+0.11) has the opposite (positive) sign, but its small magnitude may indicate that this is merely a statistical fluke.

3.2. Regional model

The impacts of school dismissal policies for the regional model are summarized in Table 2, which presents the cumulative attack rate (averaged over five stochastic realizations) and its reduction from its baseline value (without any school dismissal) under each simulation scenario. The results in Table 2 are for a shorter serial interval and "best-case" contact rates (i.e., the least plausible amount of person-to-person contact) during school dismissal (see ***Methods***); corresponding tables for the longer serial interval and/or worst-case contact patterns are provided in the SI, Tables S2-S4. From Table 2, if we compare community-wide and region-wide school dismissals of the same duration, pandemic scenarios and diagnosis ratio, the reductions of overall clinical attack rate for community-wide closures are usually higher than for region-wide closures for pandemic scenarios A, B1, B2, and D (see ***Methods*** for a description of pandemic scenarios). In pandemic scenario C, with longer school dismissals (> 4 weeks), region-wide dismissals most often have a greater attack rate reduction than the community-wide closures. Similar trends are observed whether the cumulative incidence is measured before (at day 180, Tables S5–S8) or after (at day 240, Tables 2 and S2–S4) the onset of an assumed vaccination campaign, particularly for the more transmissible scenarios B2 and D. Consequently, we will limit our subsequent discussion to the post-vaccination results based on the full 240-day simulation.

Further insight is provided by the epidemic curves for different dismissal scenarios, such as those shown in Fig. 1 for the region-wide dismissal, shorter serial interval, worst-case contact patterns, and trigger of 20 symptomatic children (i.e., dismissal upon the first diagnosed case for a 5% diagnosis ratio). Here we can see that the primary benefit of dismissals are to delay the epidemic peak, by 5–6 days per week of dismissal for most pandemic scenarios, until the peak is postponed long enough for vaccines to be introduced and reduce the spread. These delays are comparable with the ~5 days per week of dismissal recently found with a compartmental model for more severe epidemics (with a 30% baseline attack rate) (Fung et al., 2015). For the mildest pandemic scenario C, the spread is so slow and the peak so late that it is only delayed by 3–4 days per week of dismissal.

3.3. National model

For national-scale simulations, different manners of introduction of the pandemic influenza strain resulted in different disease spread dynamics. For instance, the emergence of a domestic strain from a rural area in the U.S. would likely take longer to result in widespread transmission than the importation of a novel virus from overseas which was already spreading from human to human before arriving at an urban area (where international airports are located) in the U.S. (see Figs. S7 and S8 in the SI). In addition to this, our simulation indicated that emergence of a domestic strain in a rural area had a finite probability of extinction, and its peak transmission may lag behind 1–3 months compared to that of a novel virus introduction into an urban area. For these reasons, we focus hereinafter on the results from the national-scale models that assume an overseas emergence of the novel virus with entry into the United States via air travel.

National-scale model outcomes, in terms of (symptomatic) cases averted for two pandemic scenarios (B2 and D) for different dismissal triggers, durations, and geographic scales, are presented in Fig. 2. A different view of the impacts of varying spatial extent of school dismissal is shown in Fig. 3 for pandemic scenarios B2 and D, with a 4-week closure after 20 symptomatic children appear in a community (i.e., dismissing schools upon the first detected child at a 5% diagnosis ratio). Epidemic curves are compared in the top panels for the two considered contact rate changes upon school dismissal. In the bottom panels, we show the number of schools closed over time. (These results are for the worst-case contact-rate assumption; those for the best-care contact rates are shown in Fig. S6.) As shown in Figs. S9 and S10, the reduced transmissibility of scenario C, combined with the slower spread across the dispersed U.S. population, causes it to have not yet reached its epidemic peak by the assumed availability date of an effective vaccine, six months after the first introduction. As subsequent vaccination slows and ultimately stamps out the outbreak, the effect of vaccination dominates the impact of any school dismissal and precludes any further consideration of this scenario for the national-scale model.

From Fig. 3, we observe that community-wide school dismissals reduce the peak incidence without significantly delaying the time-to-peak incidence. On the other hand, multi-county and state-wide school dismissals have more impact on delaying the time-to-peak than reducing the peak incidence. Furthermore, county-wide school dismissals have a similar time-to-epidemic-peak as multi-county and state-wide school dismissals, but with a lower peak incidence than either. These results (Fig. 2) for the effectiveness of community-wide school-dismissal strategies are consistent with the results for the regional model (see Table 2). In particular, for a low (but plausible) diagnosis ratio of 1%, waiting to close individual schools until even the first detected case may never occur. Efficacy increases with both the diagnosis ratio and duration, although a diminishing return is observed for longer dismissal durations, in particular the extended 16- and 20-week durations for scenario D. However, the chief advantage of the national-scale model is that it allows us to explore varying geographic scales of school dismissal. We find that the optimal geographic scale of school dismissal depends on the duration and trigger/diagnosis ratio (see Fig. 2). More proactive dismissals (i.e., those over broader geographic regions) are only advantageous if the closure is sufficiently long to enable vaccination, which often means a month or longer dismissal. Additionally, more proactive school dismissals over a larger geographic area (multi-county, or state level) will be more appropriate (and effective, see Fig. 2) for settings where influenza surveillance is less sensitive (i.e., where the diagnosis ratio is likely to be low).

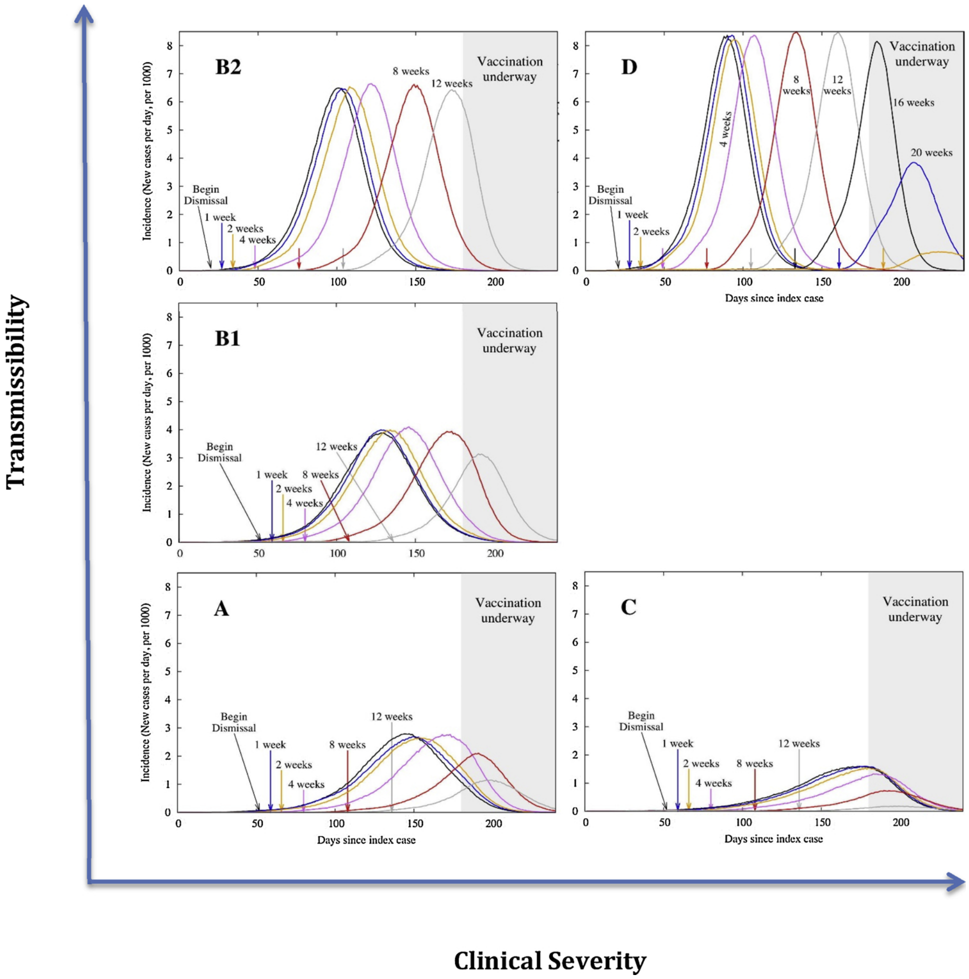

Fig. 1. Effect of school dismissal duration upon epidemic curves for simultaneous (region-wide) school dismissal for the regional model (the Chicago metropolitan area, with 8.6 M people). Results are shown for the shorter serial interval and nominal (worst-case) contact rate changes upon dismissal, activated when 20 children are symptomatic in a community (i.e., closure upon the first diagnosed case if the diagnosis ratio is 5%). Results are shown for five pandemic scenarios: four historically referenced 20th century influenza pandemics (A: 2009, B1:1968, B2: 1957, D: 1918) and a fifth scenario (C) that corresponds to a clinically severe but less transmissible pandemic.

3.4. Observations

From these regional and national model results, several observations can be made. First, the main effect of school dismissals across wider geographic scales is to slow the spread of the virus, as reflected by delayed time-to-peak, which confers multiple benefits. One is to delay and reduce peak demand for healthcare, which is particularly important at the start of a pandemic when systems are not yet prepared to deal with an ever-increasing patient load. An even greater benefit is achieved if this delay extends sufficiently long for an effective vaccine to be developed, produced, and distributed to the population (see Fig. 3). Second, the effects of school closure are very sensitive to the ability of the local surveillance system to detect influenza circulation and, in turn, provide a "trigger" for closing schools. For a diagnosis ratio as low as 1%, which might occur if laboratory confirmation is required (Reed et al., 2009), dismissals may not be triggered in time and, thus, will have no effect on morbidity (see Table 2). In contrast, when surveillance systems are able to detect 5% or more influenza cases in the community, school closures of any duration and on any scale start reducing cumulative incidence, with the effect being particularly prominent for closures lasting 8 weeks or longer (see Fig. 2).

Finally, school closures for shorter duration of closure (1–4 weeks) generally result in a greater number of cases averted at the local community level, compared to simultaneous school closures of the same duration implemented over a larger geographic area (county, multi-county, or state [see Fig. 2]). However, such simultaneous (coordinated) school closures proactively implemented over a wider region are usually superior in terms of number of cases averted if the closure is sustained over a longer period of time (8 weeks or more [see Fig. 2]). In addition, simultaneous (proactive) school dismissal policies more effectively delay the spread of the disease compared to the community-wide school closures of the same duration, albeit at the greater cost to society due to the larger number of schools that must remain closed than if the closures were implemented on an individual community-by-community basis (see bottom panels of Fig. 3). By primarily slowing, rather than reducing, the disease spread, such closures are capable of reducing the peak burden significantly if the delay extends into the time window when vaccines become available. In contrast, individual school dismissals do not have a substantial impact on when the peak burden is reached, but if implemented promptly after the occurrence of a few initial cases within a school or school district, they may help reduce its magnitude and, thus, the transitory surge on the healthcare system (see top panels of Fig. 3).

4. Discussion

The primary benefit of pre-emptive school dismissals in mitigating the spread of a novel influenza virus is the delayed time-to-peak that is seen in dismissals of any duration considered in our study, typically by 4–6 days for each week of dismissal. Delaying local outbreak peaks helps to decompress the demand on the healthcare system during the initial pandemic wave and, under certain circumstances, it may help "buy time" to prepare and roll out a pandemic vaccine. That the main effect of school dismissals is delaying the time-to-peak is fully consistent with the nature of an intervention that does not provide specific protection. Overall, longer pre-emptive school dismissals (≥ 4 weeks) implemented simultaneously on a wider geographic scale (e.g., county level or wider) are most impactful in mitigating an influenza pandemic

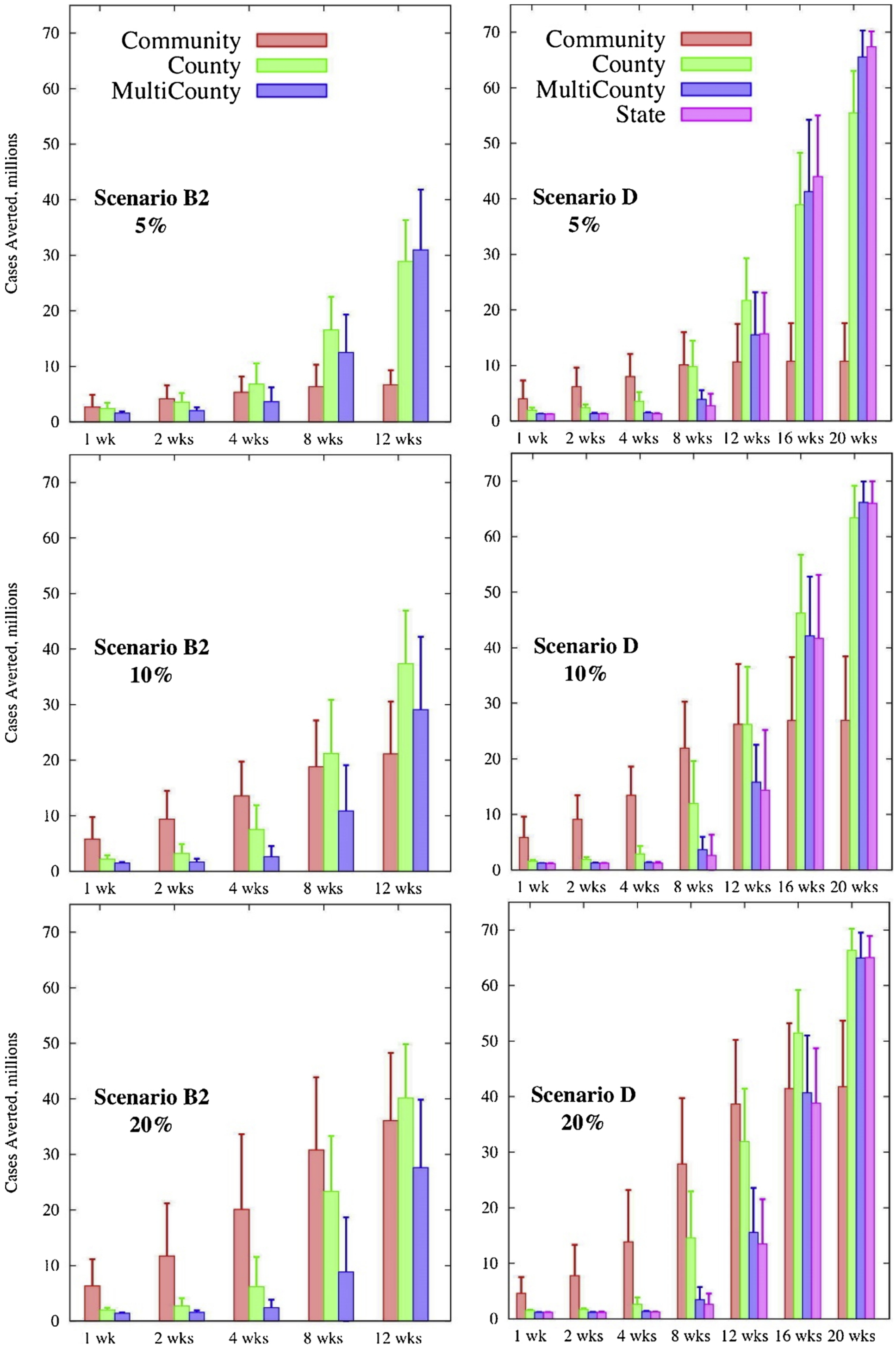

Fig. 2. U.S. model predictions of the number of (symptomatic) influenza cases averted by a combination of self-isolation, school dismissals, and vaccination, for the shorter serial interval. School dismissal is activated when one symptomatic child is diagnosed at an assumed diagnosis ratio of 5%, 10%, or 20%. Two alternative assumptions for contact rates (CR) during school dismissal are considered: "worst-case" (filled bars: CR involving children in households are doubled and child-related contacts outside the home are reduced by 30%) and "best-case" (extensions: CR involving children in households are unchanged, and child-related contacts outside the home are reduced by 50%). Beginning on day 180, 1 million people per day are vaccinated (see text and SI for details).

in its early stages, while awaiting the production and distribution of a pandemic vaccine. However, as Fig. 1 indicates, for highly transmissible strains, it may be difficult to close schools long enough to delay the epidemic peak until vaccines become available. Thus, efforts to increase the speed of vaccine production and distribution are essential to ensure that the time bought by school dismissal yields the optimal benefit (Biggerstaff et al., 2015).

In addition to delaying the time-to-peak, school dismissals of sufficient duration implemented pre-emptively on a wide-enough geographic scale may also reduce the cumulative attack rate. Our results suggest that shorter precisely targeted dismissals (1–4 weeks) implemented on an individual community-by-community basis following detection of initial cases among students at these schools appear to be superior to dismissals of the same duration implemented in a coordinated county-wide, multi-county, or state-wide manner. However, such dismissals may not be feasible in practice, as precise targeting requires prompt laboratory confirmation of initial cases in each and every community, coupled with quick dismissal of an affected school before virus spread occurs within the school and between the school and the surrounding community. For longer (multi-month) dismissals, we find that a greater reduction in cases is achieved by coordinated larger-scale dismissals (county-level or wider), being proactive rather than waiting until cases are detected in each individual community. Therefore, for the most severe pandemic scenarios, we believe that the

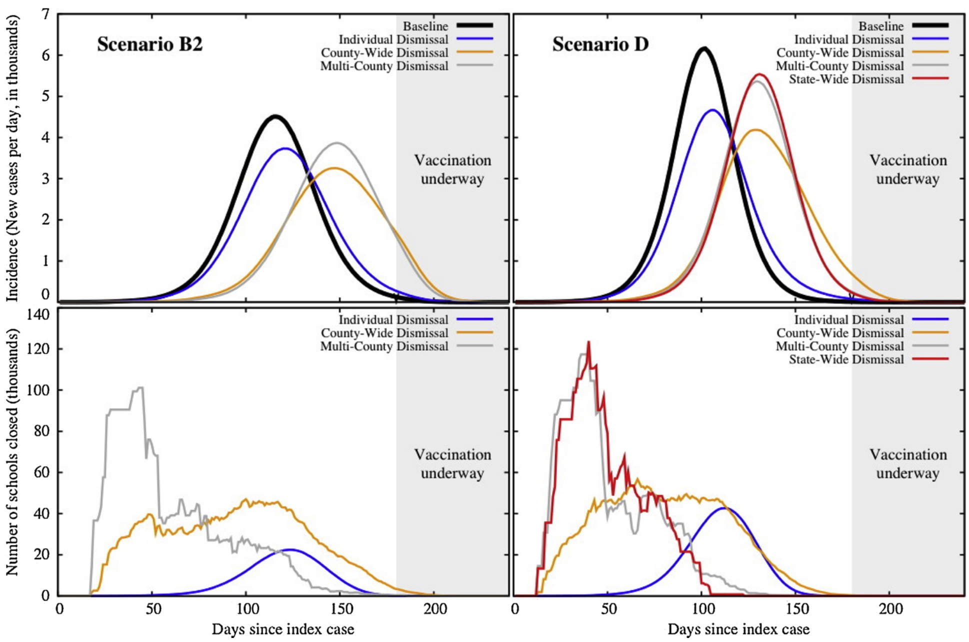

Fig. 3. U.S. model results for pandemic scenarios B2 (left panels) and D (right panels). School dismissal activated when 20 children are symptomatic (closure upon first diagnosed at a 5% diagnosis ratio) and a 4-week duration, for the shorter serial interval. (Top) Epidemic curves. (Bottom) Number of schools closed at any time during the outbreak. The “worst-case” assumption for contact rates during school dismissal is used (contact rates involving children in households are doubled, and child-related contacts outside the home are reduced by 30%). Analogous results for the “best-case” contact rates are shown in Fig. S6. Beginning on day 180, 1 million people per day are vaccinated (see text and SI for details). Note that for scenario D, the multi-county and state-wide dismissals are virtually indistinguishable, particularly for the epidemic curves.

optimal geographic unit for implementation of pre-emptive school closures as a pandemic countermeasure will be county-wide or beyond.

For less transmissible strains causing severe disease (e.g., a potential H5N1-like scenario) represented by the scenario C in our study, the effect of school dismissal on cumulative disease incidence is quite pronounced, even for shorter dismissals implemented on a narrower geographic scale. The already-low transmissibility (low R_0) in such a scenario provides an opportunity to achieve local extinction by strategically targeted and timed school closure following the initial local introduction even without vaccination. In contrast, for the most transmissible strains associated with a high clinical disease severity considered in our study (i.e., scenario D comparable to 1918), a significant reduction in cumulative disease incidence by school closure alone may only be possible when schools are out of session for 16 weeks or longer, at a county-wide or wider geographic scale. It should be noted, however, that depending on the timing of the initial pandemic waves, the effect of a long continuous school dismissal (16+ weeks) may be realized through a combination of planned school holidays and an additional dismissal (or delayed start of a semester) in response to the pandemic.

These results highlight an important practical issue, namely that the effectiveness of school dismissals is highly dependent on the local surveillance systems’ ability to quickly detect virus transmission in communities and, thus, implement (or “trigger”) the intervention in a timely fashion. Delayed detection, associated with a less-sensitive surveillance method (e.g., by waiting for laboratory confirmation) results in a delayed implementation of the intervention and, thus, a diminished effect with regard to slowing down the transmission. For a low diagnosis ratio of 1%, delaying the closure of individual schools (or communities) until a child there is confirmed is a threshold that may never be reached. (For a 2000-person community in which 22% of the population is school-aged, there are only 440 school children; it is unlikely that 100 of them will be ill at the same time.) In these cases, more sensitive triggers or surveillance approaches may be needed to ensure school outbreaks are identified promptly. Interestingly, the opposite behavior is observed for simultaneous school dismissal. In that case, the greater risk is closing (and then reopening) schools too quickly before the epidemic reaches its peak. For a low diagnosis ratio, this is the only choice, and may be the most realistic in practice: if a school has so many affected students that it is forced to close, neighboring schools will benefit by proactively dismissing. In a way, the original school (which is unlikely to benefit from closing, since it may be too late) will serve as a sentinel event, signaling the impending risk of severity to surrounding communities. Given the extreme sensitivity of the effects of school dismissals to early detection of initial cases, an aggressive surveillance system, coupled with intense pre-pandemic planning for rapid implementation of community-based interventions such as school dismissals, is needed in all settings. This may be particularly important in dense urban settings around major international hubs, where introductions of novel influenza virus strains are most probable and where an extremely high population density may facilitate transmission of strains that may be less capable of circulating in more sparsely populated areas.

To our knowledge, this is the first study that systematically explored potential effects of school closures implemented on different geographic scales relevant for the U.S. (corresponding to local, county, regional/state, and national governmental authorities) and in different pandemic severity scenarios.

Our findings are consistent with previously published studies considering school closures as the only intervention in response to an evolving pandemic. In particular, prior observational and modeling studies suggested that schools are the key community setting for pandemic influenza transmission (Chao et al., 2010; Gog et al., 2014). School closures have been found to be effective in slowing down influenza transmission, whether implemented as a mitigation strategy or due to other reasons (e.g., regular school breaks, teacher’s strike, etc.) (Earn et al., 2012; Copeland et al., 2013; Chowell et al., 2011; Heymann et al., 2004; Markel et al., 2007). In addition, other modeling studies have explored school closure as a mitigation strategy (Halloran et al., 2008; Haber et al., 2007; Milne et al., 2008; Halder et al., 2010; Lee et al., 2010; Halder et al., 2011; Brown et al., 2011; Milne et al., 2013; Fumanelli et al., 2016; De LuCa et al., 2018). However, to our knowledge, ours is the most comprehensive modeling study to evaluate the effectiveness of different school-closure strategies – including the tradeoffs between local, regional, and national dismissals – in mitigating influenza in the United States during an evolving pandemic. Model adjustments and validation were undertaken to address the research question at hand using the best currently available empirical and observational data for model parameterization, and sensitivity analyses were used to test the robustness of key findings.

As has been comprehensively reviewed by (Riley 2007) and Carrasco et al (Carrasco et al., 2013), the great flexibility of such models is also their Achilles heel, as model developers, users, and consumers often construct models and parameters in data-poor (or data-free) environments. Intentionally (as is most always the case) or not, these decisions can lead to greater confidence in model predictions than may be warranted, given their typically tenuous tie to observed truth. However, although quantitative model predictions should generally be viewed with a healthy appreciation for their limitations, in many cases, qualitative trends have been proven to be reliable and useful in pre-pandemic planning efforts (Centers for Disease Control and Prevention, 2007). We have endeavored to consider and address the key limitations that are always present in mathematical modeling studies. In the present case, the greatest uncertainty concerns how contact rates (within different mixing groups and ages) might change during the disruption accompanying an unplanned school dismissal. These will presumably vary with time (as a so-called "fear-based social distancing" gradually decays towards normal contact rate patterns), and severity (e.g., the greater case fatality ratio of pandemic scenarios C and D are more likely to lead to a greater acceptance of, and compliance with, recommended social distancing measures. Currently, to our knowledge, there are no empirical data to inform how contact patterns may change during a prolonged closure; without such data, this limitation cannot be confidently addressed. On the disease side, there remains a great deal of variability and uncertainty about the natural history of influenza, most notably its serial interval (we considered two possibilities which bracket the likely range) and the role of asymptomatic individuals in transmission (we have assumed 50% of all cases are asymptomatic; previous studies assume either 30% or 50%). As mentioned previously, the triggering of any mitigation measures is dependent upon a timely detection, while realistic diagnosis ratios for pandemic planning purposes remain uncertain (Biggerstaff et al., 2012).

In addition to testing the effects of school closures with regard to timing, duration, and geographic scale of their implementation during an evolving pandemic prior to vaccine rollout, we have performed several analyses to test the robustness of our key findings. A sensitivity and uncertainty analysis demonstrates that schools are the key community setting for influenza transmission, apart from households. Hence, reducing school transmission provides the greatest lever for slowing the disease spread before vaccination. While such analyses have rarely been performed for large, complex simulation models, many further questions remain for future research. For example, it would be important to explore to what extent the networking of multiple communities, as in our regional and national models, affects these parameter sensitivities and variability of outcomes through nonlinear effects. Since it is impossible to predict the precise characteristics of the next pandemic influenza strain, and the efficacy of potential pharmaceutical and non-pharmaceutical countermeasures, the results presented here are somewhat qualitative in nature. However, during the next pandemic, the real-time estimation of these key unknowns (a challenging task in itself) will constrain models such as those presented here, thus yielding quantitative, testable predictions.

Finally, we note that the present study also identifies several areas in which further research should be carried out. As is often the case with modeling studies, new empirical data are essential to further constrain and corroborate the models, particularly with regard to contact rates during times of social disruption, including school closures. We recognize that school dismissal incurs substantial economic and societal costs (in addition to removing a convenient location for implementing a childhood vaccination campaign), and a more complete economic analysis should be performed before recommending any specific policies. Several economic analyses of different policy options have been reported (Cauchemez et al., 2009; Halder et al., 2011; Brown et al., 2011; Milne et al., 2013; Nishiura et al., 2014), but a more comprehensive economic analysis of school closures as a pandemic mitigation strategy, both on its own and in conjunction with pandemic vaccination, would be helpful, as well as further consideration of societal options that may mitigate the secondary impact of school closures.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.epidem.2019.100348.

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